



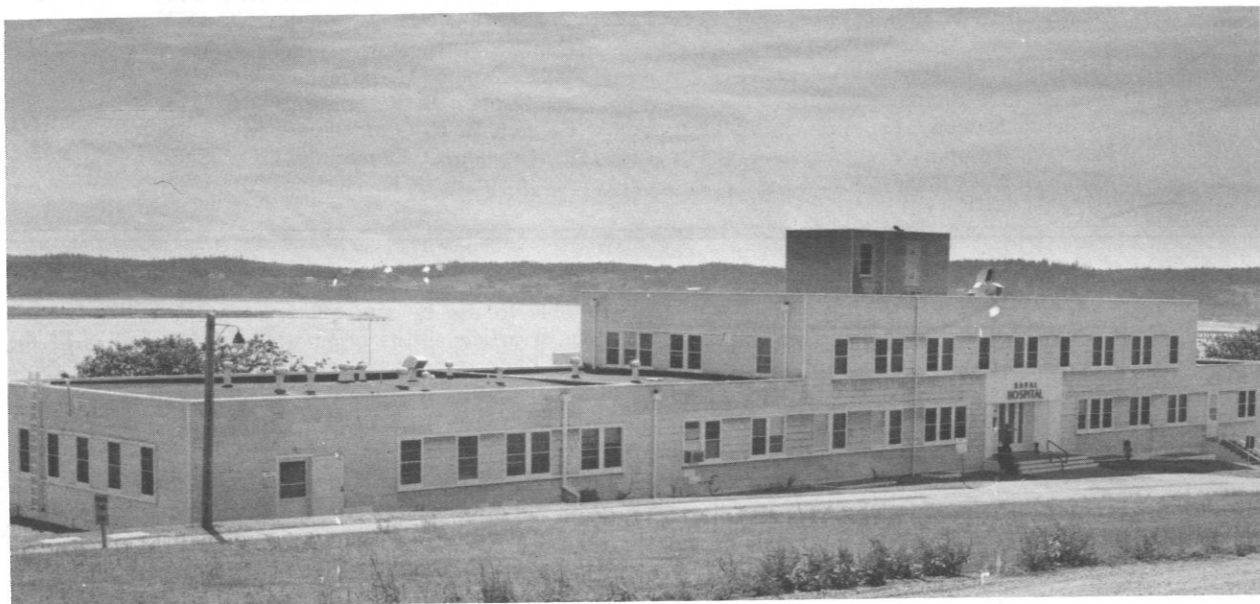
UNITED STATES NAVY *Medical News Letter*

Vol. 52

Friday, 20 December 1968

JAN 13 1969

No. 12



CONTENTS

MEDICAL ARTICLES

Carbon Monoxide	1
Genetic Predisposition to Formation of Calcium Oxalate Renal Calculi	4
Lymphogranuloma Venereum	10
Current Concepts of Snakebite Treatment	15

MEDICAL ABSTRACTS

Low Back Pain	18
Cardiovascular Screening to Assess Risk of Coronary Heart Disease	18
Strabismus	18
Host Determinants of Response to Antimicrobial Agents	19

DENTAL SECTION

Evaluation of the Navy Plaque Index	19
Photosensitive Dermatitis From Soaps	20
Personnel and Professional Notes	20

NURSE CORPS SECTION

Pediatric Conference	21
Study of Patient Attitudes Toward Older People ...	21

AEROSPACE MEDICINE SECTION

News of Personnel	22
Submission of SF's 88 and SF's 89 on Crewmembers and Noncrewmembers	23
Flight Equipment	23
Missing Survival Equipment	24
"Trip to Where"	24
Cruise Report From WestPac	24
Circadian Rhythm	26
Pulmonary Physiology	26
Blood Volume Measurements	26

EDITOR'S SECTION

Statement on Normal (Whole, Pooled) Human Plasma	27
Notice to Active Duty Medical, Dental, Nurse, and Medical Service Corps Officers	28
American Society for Hospital Food Service Administrators	28
American Board Certifications	29
In Memoriam	29

MADIGAN GENERAL HOSPITAL
MEDICAL LIBRARY
PROPERTY OF U.S. ARMY

United States Navy
MEDICAL NEWS LETTER

Vol. 52

Friday, 20 December 1968

No. 12

Vice Admiral Robert B. Brown MC USN
Surgeon General
Rear Admiral G. M. Davis MC USN
Deputy Surgeon General
Captain J. J. Downey MC USN, Editor
William A. Kline, Managing Editor
Contributing Editors

Aerospace MedicineCaptain M. D. Courtney MC USN
Dental SectionCaptain A. K. Kaires DC USN
Hospital AdministrationCaptain D. J. McLellan MSC USN
Nurse Corps SectionCDR A. M. Byrnes NC USN
Occupational MedicineCaptain N. E. Rosenwinkel MC USN
Preventive MedicineCaptain C. H. Miller MC USN
Radiation MedicineCaptain B. K. Hastings MC USN
Research SectionCaptain B. F. Gundelfinger MC USN
Reserve SectionCaptain C. Cummings MC USNR
Submarine MedicineCaptain B. K. Hastings MC USN

Policy

The U.S. Navy Medical News Letter is basically an official Medical Department publication inviting the attention of officers of the Medical Department of the Regular Navy and Naval Reserve to timely up-to-date items of official and professional interest relative to medicine, dentistry, and allied sciences. The amount of information used is only that necessary to inform adequately officers of the Medical Department of the existence and source of such information. The items used are neither intended to be, nor are they, sus-

ceptible to use by any officer as a substitute for any item or article, in its original form. All readers of the News Letter are urged to obtain the original of those items of particular interest to the individual.

Change of Address

Please forward changes of address for the News Letter to Editor: Bureau of Medicine and Surgery, Department of the Navy, Washington, D.C. 20390 (Code 18), giving full name, rank, corps, old and new addresses, and zip code.

FRONT COVER: NAVAL HOSPITAL, WHIDBEY ISLAND, OAK HARBOR, WASHINGTON. The Station Hospital at Whidbey Island, Oak Harbor, Washington was reclassified as a Naval Hospital and commissioned as such 1 July 1968. Now a BUMED command and support activity with area coordination by the Commandant, Thirteenth Naval District. The facility was originally a dispensary attached to the Whidbey Island Air Station which was established in the 1940's as an adjunct to the then existing air station at Seattle. The hospital provides inpatient and outpatient care for active duty personnel attached to the air station, and for their dependents and retired personnel. It also supports afloat personnel of aircraft carriers home-ported in the area. It provides secondary medical support to other nearby naval activities including a security group activity, a communications station, and a reserve training center. Services in preventive medicine and occupational health are provided also. Patients with chronic conditions beyond the capabilities of the hospital are transferred to the Bremerton Naval Hospital in Washington. The Whidbey Island Naval Hospital has a normal bed capacity of 33 beds, an expanded bed capacity of 45 beds, and, as of 1 August 1968, 25 operating beds.

The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

CARBON MONOXIDE

John R. Goldsmith, Science 157(3790):842-844, August 18, 1967, "Copyright 1967 by the American Association for the Advancement of Science".*

The effects of carbon monoxide on man's health are a most important and nearly neglected public problem. This was the view of participants in the Carbon Monoxide Conference, Riverside, California, 11 April 1967. The 35 scientists present agreed that carbon monoxide, in most areas, is the most important constituent to be controlled in exhaust from motor vehicles. It was agreed that the success of the efforts to control it may influence the pattern of personal and public transportation in the future. Further, it may be the carbon monoxide content of cigarette smoke which is the agent responsible for the excesses in mortality from cardiovascular disease and possibly even from emphysema and lung cancer.

There are many gaps in our knowledge of this substance. Methods are needed for measuring small amounts of carbon monoxide in humans and in experimental animals, for estimating its distribution after emission from motor vehicles and other sources, and for understanding what happens to the carbon monoxide once it is emitted into the atmosphere.

Carbon monoxide is produced physiologically in the body by the breakdown of the heme molecule; already this information has led to the recognition that, in apparatus for administering anesthetic agents by rebreathing, carbon monoxide may build up to fairly substantial levels from the amount excreted by the patient himself. The role of carbon monoxide in motor vehicle accidents is being investigated both epidemiologically and experimentally. The epidemiological investigations gain in importance because of the findings reported that persons involved in motor vehicle accidents in Paris have higher carboxyhemoglobin levels than workmen and traffic policemen who had well-defined exposures. Experimentally, many of the studies which have used simple psychomotor or reaction-time tests have appeared to indicate that the substance had little or no effect; yet it is likely that some of the psychomotor effects of

carbon monoxide exposure can be overcome by the attention of experimental subjects to the test conditions. What is more important is the effect of carbon monoxide under realistic conditions where attention may be distracted.

The meeting was opened by Hammond (American Cancer Society, New York) who pointed out that coal miners exposed largely to carbon monoxide were observed by Sayers many years ago to have an increased hematocrit. Experimentally, cigarette smokers were found to have an increase in hematocrit within minutes and also a long-term change—the former probably being due to changes in plasma volume and the latter due to the stimulus of the erythropoiesis or to delay in destruction of red cells. The short-term change is easily reversible but the long-term change only partially reversible. It has been shown that heavy smokers who have an increased hematocrit can reduce it when they stop smoking. The possibility that carbon monoxide may be involved in the mechanism is attractive. There is reason to suppose that with increased hematocrit there is an increased likelihood of clot growth; this could be a mechanism associated with the high cardiovascular mortality in cigarette smokers.

While both motor vehicle exhaust and cigarette-smoking exposures contribute substantial amounts of the substance, they have separate and distinctly different temporal patterns. Studies in cigarette-smoking beagles [*J. Am. Med. Assoc.* 199, 241 (1967)] tend to show the same effects as the studies in human smokers. Interestingly enough, the animals appear to have a hematocrit increase for the first several hundred days of experimental smoking but subsequently the hematocrit drops at about the same time that emphysema develops. It is suggested that the loss of pulmonary surface area may therefore protect against high exposures of carbon monoxide in smoking. That the same mechanisms occur in man is suggested by the increasing mortality ratio with increasing age in smokers compared with non-smokers from lung cancer and emphysema; the ratio

* Environmental Hazards Evaluation Unit, California State Department of Public Health, Berkeley.

of smoker to nonsmoker with coronary heart disease decreases with increasing age. The major defect in present experimental studies is the difficulty of determining carboxyhemoglobin from a single drop of blood.

Paul Chovin (Director of Laboratories, Prefecture of Police, Paris) described four sets of studies in Paris. The first had to do with the definition of the level of air pollution from motor vehicles; the second, with determining the extent to which policemen exposed in heavy traffic were affected by carbon monoxide; the third, the role of carbon monoxide exposures in motor vehicle drivers who were involved in accidents; and the fourth, the control of carbon monoxide in underground garages. The definition of air pollution levels was obtained by dividing the city of Paris by a rectangular grid and obtaining 317 sampling points, one in each rectangle, in or near heavy traffic. Carbon monoxide at these points was sampled in quadruplicate at the rate of 20 locations a day by using 2-liter samples taken in plastic bags for infrared analysis. Sampling locations and times were chosen to obtain evidence concerning the maximal exposure risk. These data, when averaged, produced a map of the relative intensity of air pollution in different parts of the city; the pattern is very similar for the years from 1959 to 1966. Approximately 2 percent of the values exceed 100 parts per million. The effect of increased wind speed is to reduce the average value; the effect of increased motor vehicle traffic is to increase it. Similar sampling patterns are used in road tunnels. There is a significant correlation between the length of the tunnel and the mean value of carbon monoxide obtained. There does not seem to be any increasing trend for carbon monoxide in the city as a whole during the last 6 years.

It is estimated that the average risk of people living adjacent to the streets is approximately one-third of the maximum risk obtained. The data fit a log-normal distribution with a geometric mean for 1966 of 16.6 parts per million and an arithmetic mean of about 24.6 parts per million. There is a close correlation between long-term average carbon monoxide values and atmospheric lead levels. Carbon monoxide does not correlate with benzo(a)-pyrene, however. This is interpreted to mean that lead and carbon monoxide pollution both have a common source, namely, motor vehicles, while benzo(a) pyrene is derived mostly from other sources.

A total of 331 policemen were studied while on duty for approximately 5 hours where their exposure was between 10 and 12 parts per million. Blood

samples were taken before and after the duty hours. The average increase in carbon monoxide in the blood (in milliliters of carbon monoxide per 100 milliliters of blood) was 0.024 times the average carbon monoxide exposure (in parts per million by volume) minus 0.07. The average carbon monoxide content for nonsmoking policemen was 0.28 milliliter per 100 milliliters of blood and the increase was an average of 0.11. Since the study was done during spring weather, the maximal exposure was not likely to occur during this period.

From 1959 to 1963 the municipal laboratory examined the blood of drivers who were responsible for, or involved in, accidents, usually within an hour after the accident occurred. The resulting data were compared with data obtained from town inhabitants who thought they might have carbon monoxide intoxication and with samples obtained from workmen who had some risk of exposure to carbon monoxide. The drivers as a group had substantially higher levels than either of these two populations. All three groups include smokers and nonsmokers, hence the source of the increased carboxyhemoglobin was probably the motor vehicle exhaust. Studies in Cincinnati by Brice and Roesler have shown that in 10 percent of motor vehicles there are more than 30 parts per million of carbon monoxide when the cars are in heavy traffic.

When underground garages were constructed in Paris it was found that the values of carbon monoxide sometimes exceeded 200 parts per million averaged over 20 minutes and 80 to 100 parts per million averaged over an hour. By simple adjustments of the carburetor in cars used by Paris police, a substantial decrease in emissions was produced. Before adjustment, 56.5 percent of the vehicles had exhaust with more than 4 percent carbon monoxide, but after adjustment only 8.5 percent exceeded this value. Engine adjustment is thus one way to control carbon monoxide exposures in garages. The other way, of course, is ventilation.

Following the recommendation of Frederick from Detroit, ventilation of parking garages has been required to keep carbon monoxide to less than 50 parts per million averaged over 8 hours and 100 parts per million for instantaneous measurements. The most important topics for international agreement were, according to Chovin, standardization of methods for measurement and sampling of carbon monoxide, air quality standards for motor vehicular garages, and finally, since there is much commerce in motor vehicles, efforts should be made not to encourage the marketing in Europe of cars which produce pol-

lution meeting a lower standard than is acceptable in the United States.

Goldsmith (California State Department of Public Health, Berkeley) reviewed the carbon monoxide effects which are of importance to public health. They include the interference with oxygen transport to the tissues; the possibility of increased morbidity or mortality in sensitive groups, because of interference with oxygen transport; the impairment of sensory and psychomotor functions; the possible long-term effects due to altered hematocrit or changes in the lung; and the interference with heme catabolism or production of red blood cells. He also predicted that specific enzyme and biochemical lesions would ultimately be found to be affected by carbon monoxide. The interference with oxygen transport occurs because of two reasons. One reason is the inactivation of a certain fraction of the circulating hemoglobin because of its combination with carbon monoxide. The other reason is because of the shift in the oxyhemoglobin dissociation curve in the presence of carbon monoxide. At a given level of oxyhemoglobin, oxygen is less readily given up than when carbon monoxide is lower. In recent years measurements of carbon monoxide levels in certain parts of California have been sufficiently high to suggest the possibility of increased morbidity or mortality from acute vascular episodes in sensitive segments of the population. The possibility is being investigated. Perkins (California State Department of Public Health, Berkeley) presented a study of the representativeness of the sampling station in Los Angeles which has given the most consistently high values. This was obtained by a polar coordinate grid which identified locations at the different distances and angles from the sampling point. A field team then collected grab samples systematically over the points of this grid. While there was no systematic pattern by direction or distance from the sampling point, the average of the field sample values was somewhat lower than the monitoring station, suggesting that the monitoring station was not entirely representative of the community exposure in the area.

Impairment of visual discrimination has been documented by MacFarland, and of temporal discrimination by Beard and Wertheim. Schulte has reported on the effect of carbon monoxide on complex task performance, effects being noted with a carboxyhemoglobin concentration of above 2 percent; in general, however, laboratory studies of psychomotor responses of persons exposed to carbon monoxide often fail to reveal expected changes in response. This probably is due to the ability of the

experimental subject to overcome, by increased attention, the effect which is present with exposure to the pollutant.

Since Sjöstrand had shown that the breakdown of the heme molecule will yield sufficient carbon monoxide to be readily detected in persons who have no exogenous exposure, there has been relatively little investigation of this problem until Coburn and Forster presented systematic studies of the phenomenon. It is quite possible that carbon monoxide from motor vehicle exhaust or cigarette smoking inhibits certain parts of the catabolic system and the experiments reported by Coburn and his colleagues [*J. Clin. Invest.* 46, 346 (1967)] suggest that this is occurring. It is possible, according to Goldsmith, that the role of carbon monoxide in regulating the volume of the body's circulating red cells has not been fully considered.

The problem of hemoglobin and related tetrapyrrole compound metabolism has been studied with tracer techniques by Landaw (University of California, Berkeley). In his experiments, the catalytic oxidizing substance "hopcalite" is highly efficient in oxidizing carbon monoxide. It possibly would be helpful in filters to remove the carbon monoxide from cigarette smoke. At room temperature hopcalite does not oxidize many other substances.

The desirability of large-scale, cooperative epidemiologic studies was brought up by Hammond and echoed by others. It is likely that several hundred thousand people who live and work in the same area will need to be studied in order to see what the effects of both environmental pollution and cigarette smoking might be. Among other new problems for which research is needed are the study of closed systems such as anesthesia-rebreathing systems, and even the small enclosed oxygen cribs in which newborn infants are cared for. Some of the infants with hemolytic disease may excrete fairly large amounts of carbon monoxide and thus produce important levels of carboxyhemoglobin.

For example, if the nuclear submarine *Nautilus* were submerged for 5 days and cigarette smoking or other forms of combustion were prohibited, the endogenous carbon monoxide produced by its crew members would be sufficient to exceed 25 parts per million in the vessel's atmosphere.

Schueneman (U.S. Public Health Service, Cincinnati) felt that the persons whose reactions were critical were those who spend a large portion of their lives in motor vehicles and who are cigarette smokers; exhaust control systems must be designed to protect them. However, it was pointed out that a

small fraction of the population also have unusual types of hemoglobin and those individuals might very well be unusually susceptible. Ayres (St. Vincent's Hospital, New York) pointed out that small amounts of carbon monoxide may increase the significance and severity of angina pectoris and other vascular diseases. This has been observed occasionally under controlled conditions. Myocardial oxygen consumption is substantially decreased when significant amounts of carbon monoxide are present, since the myocardium tends to extract a larger fraction of the available oxygen from the circulating blood than do other organs.

Neiberger (Meteorology Department, University of California, Los Angeles) discussed the mechanisms by which carbon monoxide is removed from the atmosphere. While these are not entirely clear, the evidence is suggestive that the substance is oxidized to carbon dioxide by either hydroxy radicals, by other oxygenated substances, or by molecular oxygen in the upper atmosphere. Xintaras (U.S. Public Health Service, Cincinnati) emphasized the need for studying the effect of carbon monoxide on sleep cycles. Many of the participants emphasized

the importance of the additional pollutants to which most people exposed to carbon monoxide are also exposed.

Ayres and Goldsmith both called attention to the ability to estimate carbon monoxide exposures in populations through the study of carboxyhemoglobin since the respiratory and circulatory system of the human is a type of integrating sampler. Estimation of carboxyhemoglobin by the measurement of expired carbon monoxide after breathholding equilibration is a very rapid, simple, and valid technique for such studies. The possibility that further research on carbon monoxide effects could well be done in athletes was stressed by Peeples (University of California, Davis). Hammond raised the question as to whether carbon monoxide was an important factor in the genesis of cancer.

The meeting was chaired by O. C. Taylor (acting director, Statewide Air Pollution Research Center, Riverside).

It was concluded that carbon monoxide may be the most underestimated pollutant of this era and the participants agreed to cooperate in further research on this subject.

GENETIC PREDISPOSITION TO FORMATION OF CALCIUM OXALATE RENAL CALCULI*

*Martin Resnick, BA, Durward B. Pridgen, BS, and Harold O. Goodman, PhD,
New Eng J Med 278(24):1313-1318, June 13, 1968.*

Though genetic factors have been recognized as primary determinants of the tendency to form cystine and uric acid stones the role of heredity in the more common types of kidney stones remains uncertain. Previous case reports tend to be biased in that families with unusually large numbers of members with the diathesis are more likely to be reported. In the only large sample genetic study known to us, McGeown found a significant excess of members with a tendency to stone formation among the parents and siblings of her 174 probands as compared to relatives of her controls. However, she did not test for mode of inheritance. Furthermore, her

data on relatives were obtained from a single informant per family, and the accuracy of the information obtained was not assessed.

Several factors complicate the genetic study of renal calculi, including wide variability in ages at onset, possible etiologic heterogeneity, potential bias in hospitalized patients with tendency to stone formation in relation to those not hospitalized for treatment, the increased probability of detecting a family if it has many than if it has fewer members prone to calculi formation and the lack of information one member may have of disease in another member of the same family. Though the foregoing is not an exhaustive list of potential biases, it includes those most likely to produce misleading inferences. The present study was designed to obviate or permit the assessment of as many of these influences as seemed feasible.

* From the Departments of Preventive Medicine and Genetics and Urology, Bowman Gray School of Medicine (address reprint requests to Dr. Goodman at the Department of Preventive Medicine and Genetics, Bowman Gray School of Medicine, Winston-Salem, N.C. 27103).

Supported in part by a grant (HD-02206) from the National Institutes of Health and by a grant from the John A. Hartford Foundation, Inc., New York, N.Y.

Subjects and Methods

Selection of Propositi and Controls

To minimize etiologic heterogeneity and the potential bias in hospitalized subjects, propoiti were selected from the stone-analysis laboratory of Bowman Gray School of Medicine. Stones are submitted for analysis from western North Carolina and more distant points, but subjects need not be hospitalized. Cards were selected from this file on the basis of two criteria: the analysis must have revealed calcium oxalate as the major constituent of the stone; and the subject must have resided within one of four counties contiguous to this institution (to minimize the expense of field work). To obtain subjects for whom a relatively recent address would be available, only cards reporting analyses between May 1, 1961, and April 31, 1966, were selected. Random numbers were assigned to each card meeting these criteria, and the propoiti were drawn for study according to these numbers.

The control subjects were the relatives of spouses of stone-forming propoiti. The spouses' relatives will generally match those of the propoiti for age and for a variety of factors (such as socioeconomic status, residence and occupation) better than any alternative control known to us. Furthermore, they escape the potential bias in selection of hospitalized subjects with other diseases.

Data Collected

We started the collection of data by arranging a personal interview with the stone-forming propoitus and his or her spouse. At that time the names, ages, sexes and addresses of the parents, siblings and offspring were recorded. In addition, subjects were asked which of these relatives also had kidney-stone disease. Similar information was obtained about the spouse's relatives. A medical-history questionnaire was also completed for the propoitus and his spouse. This questionnaire asked for the subject's name and date of birth, the name and address of the family physician or last physician visited, seven questions about kidney disease (for example, whether the subject had had kidney colic, kidney infections or pain on urination), and whether the subject had had surgery for removal of a stone or medical treatment for stones.

To minimize the possibility that cases of stone disease in other relatives might not have been known to the first informants, an explanatory letter and the same medical questionnaire mentioned above were sent to each parent and sibling of propoiti and con-

trols. If the questionnaire was not returned within three weeks, a follow-up letter was sent. A third letter was sent to those not responding to the questionnaire and first letter. Telephone calls and personal visits were made when correspondence produced no response. A death-data questionnaire comparable to the medical-history questionnaire was sent to a parent or sibling of each deceased relative; this questionnaire was sent to the surviving spouse if the deceased had had children.

The information obtained from relatives was validated from physicians' or hospital records when possible. Some physicians were dead, and their records were not available. In other cases only the physician's recall of the patient's stone episode was obtained. Death records were searched but did not provide any information not already obtained from relatives or records of physicians or hospitals. Relatives who reported stone disease were asked if they had saved a stone and, if so, whether they were willing to permit analysis of the stone. Chemical analyses were performed on the specimens obtained.

Results

A total of 257 cards meeting the criteria specified above were found. Out of 137 subjects randomly selected from this total, 28 were not studied for the reasons given in Table 1. Fortunately, few were unwilling to co-operate, most losses occurring because subjects moved out of the area or because we were unable to locate them. No rigorous efforts were made to locate those for whom the most recent address was no longer apparently correct.

The 106 propoiti comprised 82 males and 24 females; all were Caucasian. The predominance of males is significantly different from the 2:1 ratio of males to females often observed among oxalate stone formers ($X^2 = 5.46$, p less than 0.05), but since the proportions were not significantly different from the ratio in the sample of 257 subjects from which the propoiti were drawn (198 males and 59 females), no effort was made to match a particular ratio.

The number and proportions of relatives for whom a medical history or death-data questionnaire was obtained are given in Table 2. It was anticipated that control relatives would be less willing to respond than relatives of propoiti, and, in general, a greater effort was required for the data obtained. However, the high proportion of response from both propoiti and control relatives suggests that inferences drawn cannot be heavily biased by incomplete reporting.

TABLE 1. *Number of Propositi Selected and Reasons for Losses of Potential Propositi*

Group	Number
Total cards meeting study criteria	257
Total sample drawn	134
Propositi studied	106
Propositus could not be located	13
Propositus moved out of area	11
Propositus refused to co-operate	3
Brother of propositus previously selected	1

The use of relatives of spouses as controls was predicated on the expectancy that ages of these persons would be comparable to those of relatives of propositi. The means and variances of ages of corresponding relatives in the two groups were tested, and no significant differences were detected. The mean and variance for brothers of propositi were 43.1 and 154.2 years respectively, corresponding statistics for control brothers being 42.8 and 152.2. Comparison of the same statistics for other relatives revealed similarly minute differences. Hence, comparisons between relatives of propositi and controls did not require age adjustments.

For all analytic purposes, it was assumed that when an informant said that a stone had formed he was not mistaken. The one third of reported cases of stone disease that were validated from physicians' or hospital records were correct with the exception of one woman who reported stones that the records revealed to be gallstones. Most of the remaining cases were not validated because the physician or hospital was out of the immediate area or the addresses provided by informants were inadequate. Furthermore, the accuracy of the reports of stones that were validated discouraged the extensive correspondence entailed in checking all reports. Hence, the validity of these findings depends on each informant's knowledge of whether or not he had had kidney-stone disease.

Completeness of Reporting and Frequency of Stones

To assess errors of reporting, the first informant's statement about kidney stones in a given relative

TABLE 2. *Number and Proportion of Relatives of Propositi and Controls for Whom Medical-History or Death-Data Questionnaires Were Received*

Relatives	Relatives of Propositi			Control Relatives		
	No. sent	No. Received	% Received	No. sent	No. Received	% Received
Fathers	106	96	90.6	99	87	87.9
Mothers	106	97	91.5	99	89	89.9
Brothers	205	180	87.8	185	144	77.8
Sisters	208	181	87.0	193	150	77.7

was compared to information received from that relative. As might be expected, errors tended toward under-reporting, only five errors being falsely positive (one father and two brothers among relatives of propositi and one father and one sister among control relatives). Of 87 cases found among relatives of propositi, 17 (19.5 percent) were not reported by first informants. Similarly, first reports of stones in six of 29 (20.7 percent) controls were falsely negative. The frequency of these errors suggest that data from first informants about stone formation in persons from whom responses were not obtained may be used without introducing gross error. For instance, among the 25 brothers of propositi from whom questionnaires were not received, three were reported to have stones. With correction for 20 percent under-reporting, 3.8 of these brothers would have been expected to report stones if they had responded. Considering the proportion with stones among responding brothers, 39 out of 180 (21.7 percent) reported at least one stone. If the same proportion had been assumed for nonresponding brothers, 5.4 should have had stones. Since neither of these estimates differs by more than sampling error from the three brothers among nonrespondents reported to have stones, we have assumed for analytic purposes that information received about nonrespondents from their relatives was accurate.

Stone disease was significantly more frequent among the fathers and brothers of propositi than among corresponding control relatives and was also more frequent among mothers and sisters, but the differences did not reach conventional significance levels as shown in Table 3. However, when the control families of spouses who formed stones were excluded, the mothers and sisters of propositi also had significantly more stone disease than corresponding control relatives ($X^2 = 6.17$, p less than 0.02, and $X^2 = 5.85$, p less than 0.02 respectively). Only two children of propositi had formed stones. The children were generally too young for many to have formed stones and were recorded for possible future study only.

Stones that had been saved were obtained from 30 subjects, including 17 propositi who had saved a stone formed after the analysis performed in this laboratory, two parents and 11 siblings. All contained calcium oxalate as a major constituent. Two stones were obtained from control relatives, one from the spouse of a propositus (calcium phosphate) and a calcium oxalate stone from a control brother. These few data are in keeping with previous indica-

TABLE 3. Frequency of Renal Calculi among the Parents and Siblings of Propositi and Corresponding Control Relatives

Relatives	Propositi			Controls			X ²	P Value
	Normal	Affected	% Affected	Normal	Affected	% Affected		
Fathers	90	16	15.1	94	4	4.1	6.98	<0.01
Mothers	94	12	11.3	95	4	4.0	3.77	<0.10
Brothers	163	42	20.5	172	13	7.0	14.51	<0.001
Sisters	191	17	8.2	185	8	4.1	2.78	<0.10

tions that, barring concurrent infection, stones formed within family groups tend to be similar in chemical composition.

The cases of stone formation listed in Table 3 included three parents and three siblings of propoiti who formed vesical stones (6.9 percent of all stones). One of the 29 controls with stones also formed a vesical stone. These were included with those forming renal stones in all analyses.

Control families were not available for seven propoiti because the propoitus was either single, widowed or divorced and it was not possible to establish contact with the previous spouse's family. The frequency of stone formers in the general population leads one to expect some spouses to have stones. Among the 99 control spouses, six out of 78 females and two out of 21 males had formed kidney stones.

Stone Formation in Control Families

We were curious to determine whether the frequency of stones among control families including at least one member with stones was comparable to data obtained from the relatives of the propoiti with stones. Considering first the eight families in which the control spouse had stones, the frequencies of stones among parents or siblings (excluding control spouses) were not significantly different from those found among corresponding relatives of stone-forming propoiti. Similarly, among the 19 families in which at least one parent or sibling of a spouse had stone disease but the control spouse was not affected, the frequencies for control relatives did not differ from those among the relatives of the propoiti. In all other testable regards (such as age at onset and sex differences) the families with stone disease among the controls were comparable to the families of propoiti with stones. These findings suggest that whatever genetic factors are involved in stone disease, they are similar among control families with stones.

Tests for Monogenic Inheritance

The excess of stone formation found among the first-degree relatives of propoiti supports the in-

ference that genetic factors regulate the tendency to calcium oxalate stone disease but does not indicate modes of inheritance. The obvious sex difference in the frequency of stones suggests that X-linked factors may be involved or that age at onset may be significantly delayed in females. No significant sex differences in ages at onset were found in either the parental or sibling generations. X-linkage should give rise to distortions in the sex ratio of affected siblings in families with an affected father as compared to those with an affected mother and in families ascertained through male as compared with those ascertained through female propoiti. However, tests of sex ratios among affected offspring of affected parents and among affected sibs of male and female propoiti exhibited no distortion compatible with X-linked inheritance, suggesting that X-linked genes do not participate directly in the diathesis.

Autosomal dominant inheritance appears to be a most inviting hypothesis because some parents are affected, and it is possible that other parents would be genetically susceptible but have not yet expressed their diathesis in frank disease. In one effort to determine whether this hypothesis was tenable, life-table calculations were used to estimate the number of stones that would develop among male sibs of propoiti if all male sibs alive lived to the age of 75. In the absence of suitable data to estimate the age-specific probability that stones would develop within a given age interval, the past experience of these male siblings was used. These calculations suggest that an additional 57.5 male sibs should form stones. When combined with the 42 who have already formed stones, the total frequency $(99.5/205) \times 100 = 48.5$ percent approached the 50 percent expected if an autosomal dominant gene had been involved. A rough correction for mortality indicated that in no less than 40 percent stones would develop even if those who died without having stones were taken into account. However, when the probabilities that stones would develop in male sibs were applied to their fathers' experience 49 cases of stone disease would have been expected, in contrast to the 16 cases observed. Similar calculations for females were not

possible because of the few cases of stones, but, again, the frequency of stones among mothers of propositi, considering their longer exposure to risk, was much too low in relation to the female siblings to support autosomal dominant inheritance.

Autosomal recessive inheritance with lower penetrance in females is a possible alternative, but one would expect a higher proportion of children with stones when one parent is affected than when both parents are normal by a factor of two. Though more siblings form stones when one parent is affected (26.1 percent of males and 14.3 percent of females compared to 18.9 percent of males and 6.6 percent of females when both parents free of stones), the difference is not of the expected magnitude, and tests of these proportions for the two sexes separately detected no significant differences ($X^2 = 2.62$, p less than 0.05, and $X^2 = 1.14$, p less than 0.10 for males and females, respectively). Furthermore, the test for polygenic inheritance described below tends to rule out recessive as well as dominant inheritance.

Test for Polygenic Inheritance

The only hypothesis remaining of the hypotheses commonly tested is that of polygenic inheritance. As pointed out by Edwards, polygenic inheritance can often simulate monogenic inheritance, especially if the condition being studied is common. The operational similarity of inheritance due to a common autosomal recessive gene and polygenic inheritance makes distinction of the two difficult. One test to distinguish monogenic from polygenic inheritance is to examine the frequency of affected younger sibs among families in which an older sib in addition to the propositus is affected. If the disease is polygenic, the risk will be higher for these sibs than for those in families in which an older sib is not affected. In monogenic inheritance, on the other hand, the risk will be the same for younger sibs regardless of whether an older sib is affected. It was apparent from our data that too few stones occurred among the oldest sibs to permit a decisive test to be made, since in 63 families the oldest sib was normal and was affected in only 17 families (the remaining sibships had too few siblings for this test). With the two oldest sibs as a criterion (excluding the propositus in all cases), sibships were separated according to whether the older two sibs were both normal, one normal and one affected or two affected. The siblings listed in Table 4 do not include either the propositi or the two older siblings on whom selection was based. If one considers the males only and pools

TABLE 4. *Number of Normal and Affected Younger Sibs According to the Condition of the Two Oldest Siblings (Excluding Propositi)*

Condition of 2 Oldest Siblings	Younger Siblings						Total % Affected
	Male			Female			
	nor- mal	af- fected	% af- fected	nor- mal	af- fected	% af- fected	
Both normal	60	7	10.4	75	2	2.6	6.2
1 normal; 1 affected.	34	11	24.4	32	3	8.6	17.5
Both affected	8	2	20.0	1	1	50.0	25.0

those few from the affected-affected pairs with those from the affected-normal pairs, the difference is significant ($X^2 = 3.83$, p less than 0.05). When the affected-affected are pooled with the affected-normal class and sexes pooled as well, the excess of younger affected sibs in these groups is highly significant ($X^2 = 8.56$, p less than 0.01). Though a possible source of bias is selection for older sibships, calculations showed that the difference did not arise in this way. Hence, these data suggest that a polygenic rather than a monogenic system is responsible for the tendency to calcium oxalate stone formation.

The method of Falconer may be used to estimate heritability (h^2)—that is, the additive genetic variance as a proportion of the phenotypic or observed variance. The estimate based on male siblings of propositi and controls, $h^2 = 63 \pm 14$ percent, does not differ significantly from his estimate for calcigerous stones based on McGeown's total data, $h^2 = 46 \pm 9$ percent. Though these estimates are comparable, they do not separate the effects of correlations in environmental components within families as recognized by Falconer, and, hence, tend to overestimate heritability. They are also complicated in stone disease by sex differences, changes in incidence with age and possible genetic heterogeneity in McGeown's data (as indicated below).

Homogeneity, Recurrence and Infections among Stone Formers

The foregoing analyses do not permit detection of possible heterogeneity in the etiology of stones within these family groups. It is possible that both different genetic constitutions for stones and varying environmental factors could lead to a high risk of stones in some families and a much lower risk in others. Such an outcome would make it unlikely that a single genetic hypothesis could explain the diathesis. One test for such heterogeneity is to compute the expected numbers of stones in sibship of various sizes on the assumption of a uniform proba-

bility that stones will develop in all sibships. Analysis was based on male siblings, the only group large enough to permit a meaningful test. When expected numbers computed from the binomial expansion were tested against observed numbers, no significant differences were detected. Hence, these data provided no evidence of genetic heterogeneity.

The data were examined to determine whether the frequency of single and recurrent stone formation among relatives was different when probands had had a single stone or had had recurrent stone disease. The data for mothers suggests a possible association, but the differences were not statistically significant. Data for the largest group, the siblings, do not indicate that relatives of persons with recurrent stone formation have an increased likelihood of recurrent rather than single stone formation.

Reports of urinary-tract infections were tabulated though it was apparent that some respondents had failed to fill out this section of the medical history questionnaire. Obviously, some may not have been aware of infections that they may have had. The stone-free relatives of probands and controls reported comparable numbers of urinary-tract infections. The well known association between stones and urinary-tract infections is reflected in the fact that significantly more infections were reported by those of both sexes with stones though 69 percent of males and 48 percent of females with stone formation did not report infections. Comparisons of the frequency of infections among persons with single and those with recurrent stone formation revealed no significant differences in either sex.

Discussion

The hypothesis of polygenic inheritance to account for the tendency to calcium oxalate stone formation implies that at least two (and probably more) gene loci influence susceptibility. Since the genotype is fixed at conception, genetic and environmental factors must obviously operate for some time before frank disease results. The analyses performed above do not separate the effects of environment from those of genetic factors and, of course, do not help us in the identification of environmental factors. However, the environmental factors are almost certainly multiple as evidenced by the variety of diseases that can precipitate stone formation.

The work of Edwards showed that a relation exists between the frequency of a polygenic trait among relatives of persons with the trait and the frequency in the general population. The frequency among first-degree relatives is the square root of the popula-

tion frequency. Hence, squaring the frequency among first-degree relatives provides an estimate of the population frequency. From brothers of probands one would estimate the population frequency to be $(42/205)^2 = 0.042$, or four and two tenths per 100 adult males. The estimate from fathers— $(16/106)^2 =$ two and three tenths per 100—is not much lower. The frequency of stones among the unselected male control spouses was two of 21 (9.5 percent). The estimate of population incidence for females based on sisters is $17/208^2 = 0.007$, or 7 per thousand, and based on mothers is 1.3 percent. Six out of 82 female spouses of probands formed stones. The observed frequency for both male and female spouses would be expected to exceed the estimates based on the incidence in relatives because the stone disease observed among spouses included all types of stones whereas the population estimates would apply to calcium oxalate stones only. The few cases among spouses suggest that more than half the renal stones in males and a still greater proportion in females in the general population are not calcium oxalate, but no data are available for comparison. The only stone that we obtained from a spouse revealed calcium phosphate on analysis.

As expected, all estimates are much higher than those reported for hospital samples. On the basis of a hospital survey, Boyce, Garvey and Strawcutter estimated that 14.4 per 10,000 population were admitted to hospitals in North Carolina for calculi. In the same study, they point out that 85 percent of all patients with urinary calculi have a single small stone that may be passed spontaneously or with the aid of cystoscopic manipulation. Many of our subjects with stones were never hospitalized for stone disease, and some with recurrent stone formation did not even visit a physician when a stone passed after their first attack. Hence, it is not surprising that the estimates of stone in the general population far exceeds the frequency found among hospital admissions.

The incidence of stones among relatives of probands in this study significantly exceed those reported by McGeown. Under-reporting and geographic and ethnic differences may account for some of this difference. However, a larger proportion of the difference may be due to differences in selection of probands. McGeown studied persons with calcigerous stones (including phosphate and oxalate types) whereas we studied only those with oxalate stone formation. Thomas et al. found that 37.8 percent of persons with calcium oxalate stone formation had at least one other with stone forma-

tion among their first-degree relatives whereas only 9.5 percent of those with phosphate stones had affected relatives. McGeown's data could have included enough persons with phosphate stones to explain the differences in the two studies.

If the hypothesis of polygenic inheritance is correct, one implication for future research is that no single biochemical variable that will account for the tendency to oxalate stones, at least, is apt to be detected. Rather, it suggests that two or more variables that combine to produce the diathesis will be found. The polygenic hypothesis implies that the genetic constitution for stone formation is the same in both sexes, and that only the threshold differs. An analogous situation appears to prevail in congenital pyloric stenosis, in which the threshold is also higher in females.

The most significant test in this study is the one distinguishing polygenic from monogenic inheritance.

We were lucky to have detected the difference because the power of this test calculated from the same data was only 0.61. In other words, if the "true" difference was that observed, about 40 percent of samples of comparable size from this population would have failed to detect the difference. Hence, it would be important in corroborating this study to obtain a larger sample since failure to find a similar significant difference in samples equal to or smaller than the present one could not be considered contradictory.

We are indebted to Dr. William H. Boyce for encouragement and support, to Drs. C. Nash Hernndon and J. Stanton King, Jr., for stimulating discussions and for a critical reading of the manuscript and to Mrs. Annette Dawkins, Annette Schiller and Sharon Hudler for valuable technical assistance.

(The references may be seen in the original article.)

LYMPHOGRANULOMA VENEREUM

MAJ Arthur J. Abrams, MC USA, JAMA 205(4):199-202, July 22, 1968.

The incidence of lymphogranuloma venereum in the United States is increasing. A large segment of this increase is due to dissemination of the disease by American soldiers returning from Southeast Asia. Seventeen of 20 patients seen at a large military hospital had the triad of typical inguinal or femoral adenopathy, positive Frei test, and significant complement fixing antibodies; however, no correlation was found between the clinical severity of the disease and quantitation of the test results. A 21-day course of either tetracyclines or sulfonamides was equally effective in eradicating the disease in all but one case. Aspiration of fluctuant nodes to prevent rupture proved an effective therapeutic adjunct.

Lymphogranuloma venereum (LGV) is a systemic disease acquired primarily through sexual contact with infected individuals. Clinical findings center about the genital, inguinal, perianal, and anal areas. Systemic signs and symptoms may occur simultaneously. Although LGV was uncommon in the United States, there has recently been an upsurge

in the number of cases. In a 20-month period (November 1965 to June 1967) at Letterman General Hospital, San Francisco, LGV was clinically diagnosed in 29 patients. Twenty cases have been selected for this study: 18 male military, recent returnees from Vietnam; one male military, a recent returnee from Europe; and one woman, a sexual partner of a Vietnam veteran. All patients presented when LGV was in its early stages. Nine patients were transient personnel, and were eliminated from the original group because of insufficient data.

The influx of LGV has prompted this presentation of the clinical, diagnostic, and therapeutic features of the disease.

Materials and Methods

The patients, 6 white men, one woman, and 13 Negro men, ranged in age from 21 to 42 years. Initially the diagnosis was suspected on clinical grounds in patients with inguinal adenopathy and/or femoral adenopathy, with or without genital lesion. After identification of LGV in the first seven patients, a questionnaire was used to aid in categorizing the findings in other patients for this study. Patients hospitalized had complete physical examinations.

From the Dermatology Service, Department of Medicine, Letterman General Hospital, San Francisco. Major Abrams is now with the 249th General Hospital, APO San Francisco.
Reprint requests to 249th General Hospital, APO San Francisco 96267 (MAJ Abrams).

TABLE 1. *Systemic Symptoms on Initial Examination **

Total Percent Case No.	Fever 11 55	Malaise 5 25	Head- ache 4 20	An- orexia 4 20	Stiff Neck 2 10	Arth- ralgia 1 5	Chills 3 15	Light- headedness 1 5	Night Sweats 1 5
1	+	+	—	—	+	—	—	—	—
2	+	—	—	—	—	—	+	—	+
3	+	+	—	+	+	—	—	—	—
6	+	+	—	+	—	—	+	+	—
7	+	+	+	—	—	—	+	—	—
8	+	+	+	+	—	+	—	—	—
10	+	—	—	—	—	—	—	—	—
14	+	—	—	—	—	—	—	—	—
16	+	—	—	—	—	—	—	—	—
17	+	—	+	—	—	—	—	—	—
18	—	—	+	+	—	—	—	—	—
19	+	—	—	—	—	—	—	—	—

* Eight patients (cases 4, 5, 9, 11, 12, 13, 15, and 20) were asymptomatic.

† + signifies symptom was present; — signifies symptom was absent.

Examinations of patients treated in the clinic were limited to the inguinal, genital, and anal areas, unless the individual's history indicated a need for more extensive evaluation.

The following laboratory tests were performed: LGV complement fixation (CF) test, which was repeated three weeks later; Frei skin test, which was repeated one to three weeks later on all patients whose reactions were initially negative; complete hemogram; protein electrophoresis; a serologic test for syphilis (STS); and fluorescent treponemal antibody test (FTA) on all patients with reactive STS.

Drugs, supportive therapy, and selective surgical procedures were used in care of the patients. Two drugs were used over a 21-day course: tetracycline hydrochloride, 500 mg every six hours; or sulfisoxazole, 4 gm loading dose, followed by 500 mg every six hours; or a course of both drugs. Supportive therapy consisted of bed rest and cool compresses to involved areas. Obviously suppurative nodes were aspirated to prevent spontaneous rupture. The aspirations were performed by inserting a No. 20 gauge needle through adjacent normal-appearing skin rather than directly through the skin overlying the nodes.

Patients were considered ready for discharge when they had completed the course of therapy, were asymptomatic, and the nodes, although palpable, were firm and had not reduced further in size during the last seven days of therapy. Physical examination and laboratory studies were maintained to confirm therapeutic success.

Results

Twelve (60 percent) of the 20 patients (average age 25 years; 19 men, one woman) presented sys-

temic symptoms, particularly fever, on the initial examination. Eight (40 percent) were asymptomatic (Table 1).

Eight of the 20 patients (40 percent) had a genital lesion. The lesions were characterized as ulcer (five cases), nodule (one case), urethritis (one case); and a nondescript rash (one case). No primary anal lesions were found (Table 2).

Every patient had inguinal or femoral adenopathy at some time during the course of the disease. The adenopathy varied from insignificant nodules to draining sinuses. Four patients had bilateral adenopathy; ten had involvement on the right side; six had involvement on the left. A groove corresponding to the inguinal ligament, separating the inguinal from the femoral group of nodes, was noted in four cases. Prior to examination and treatment of three of the patients on the Dermatology Service at Letterman, one case (case 13) had been diagnosed as hernia and the nodes excised; one (case 18) had been diagnosed as inguinal abscess and the nodes widely incised; and in one patient (case 3) the nodes had spontaneously ruptured (Table 2).

There was one incident each of perirectal abscess with fistulous tracts leading to the base of the scrotum (case 5); hepatosplenomegaly (case 7); and transient monoarticular arthritis (case 8). The woman (case 15) had no complaints referable to the anorectal area. No genital elephantiasis was seen in this series.

Titers ranged from 1:10 to greater than 1:320 with the LGV complement fixation test. Fifteen patients (75 percent) had positive titers (1:10 or greater) on the initial test. Titers became positive in three patients who initially had negative CF tests, and who were available for a second test three weeks

TABLE 2. Clinical Information

Case No.	Primary Lesion	Regional Adenopathy	Inguinal Groove	Drug Therapy
1	None	Right	Yes	Tetracycline
2	None	Left	...	Tetracycline
3	None	Right, aspirated (ruptured)	Yes	Tetracycline and sulfisoxazole
4	Urethritis*	Bilateral	No	Sulfisoxazole
5	None	Left, aspirated	No	Tetracycline and sulfisoxazole
6	None	Left	No	Tetracycline
7	"Rash"†	Left, aspirated	No	Tetracycline
8	None	Right, aspirated	...	Tetracycline
9	None	Right	No	Tetracycline
10	Ulcer*	Right	Yes	Tetracycline
11	Nodule*	Bilateral	No	Tetracycline
12	None	Left	Yes	Sulfisoxazole
13	None	Right, excised	No	Tetracycline and sulfisoxazole
14	Ulcer*	Right	No	Sulfisoxazole
15	None	Left	...	Sulfisoxazole
16	Ulcer*	Bilateral	No	Tetracycline and sulfisoxazole
17	Ulcer*	Right, aspirated	...	Tetracycline
18	None	Right, incised	No	Tetracycline
19	None	Right	No	Sulfisoxazole
20	Ulcer*	Bilateral	No	Tetracycline

* Type of lesion was determined by physical examination.

† Type of lesion was determined by history, as reported by patient.

TABLE 3. Test Results

Case No.	LGV CF Test Titers*		Frei Test		STS	FTA
	Initial	Repeat	Initial	Repeat		
1	Positive †	...	Negative	...
2	1:40	1:10	Positive	...	Negative	...
3	1:10	1:20	Positive	...	Negative	...
4	1:20	1:20	Positive	...	Negative	...
5	1:40	1:40	Positive	...	Positive	Negative
6	1:40	...	Negative	Positive
7	1:40	Negative	Negative	Positive	Negative	...
8	1:20	1:40	Positive	...	Positive	Negative
9	Negative	...	Positive
10	Negative	1:20	Positive	...	Negative	...
11	1:10	1:20	Positive	...	Negative	...
12	1:40	...	Negative	Positive	Positive	Positive‡
13	Equivocal	...	Positive	...	Negative	...
14	1:20	1:20	Negative	Positive	Negative	...
15	Negative	1:20	Negative	Positive	Negative	...
16	1:10	1:20	Positive	...	Negative	...
17	1:40	1:20	Negative	Equivocal	Negative	...
18	>1:320	1:80	Positive	...	Negative	...
19	1:20	...	Negative	Positive	Positive	Negative
20	Negative	1:20	Negative	Positive

* A titer of 1:10 or greater was considered positive.

† Positive signifies a papule 6 mm or greater; the control, 3 mm or less.

‡ Diagnosed as latent syphilis.

later. One patient was not available. Only two patients (cases 7 and 18) showed significant changes in titer after the three-week course of therapy (Table 3).

Nineteen (95 percent) of the patients in this study had positive Frei tests: twelve had positive reactions to the Frei test on the initial injection, and the reactions of seven converted to positive on the second test, one to three weeks later. One patient

(case 17) had an allergic reaction to the control material so that Frei test could not be interpreted (Table 3). Positive reactions varied from an induration 6 mm in diameter to one 14 mm in diameter. The size did not correlate with the severity of the clinical manifestations. A serologic test for syphilis was performed for 17 of the patients; 4 had a positive reaction. Three of these patients had negative responses to the FTA. The one positive

response to the FTA was considered due to latent syphilis.

The study reveals that 17 of the 20 patients (85 percent) had clinical, skin test, and CF titer evidence of LGV. In three patients (cases 1, 9, and 13) the clinical symptoms and Frei test were compatible with the diagnosis; however, one or more complement fixation tests were not recorded (Table 3).

Eleven of the patients (55 percent) received tetracycline, five (25 percent) received sulfisoxazole, and four (20 percent) received both drugs (Table 2). The drugs appeared to be equally effective therapeutically.

Two patients (cases 14 and 19) had elevated white blood cell counts (WBCs) while seven had abnormal differential counts. The monocyte count ranged from 7 percent to 15 percent (average 12) in these cases. The erythrocyte sedimentation rate (ESR) was elevated in 12 patients with a range of 21 to 45 mm/hr (Wintrobe). The ESR was not recorded in three cases and was normal in five cases. Results of protein electrophoresis were abnormal in eight cases and were not recorded in three cases (Table 4).

Aspiration of the nodes was necessary in five cases (25 percent). There were no complications following the aspirations or the other surgical procedures (Table 2). Nodes were studied microscopically following excision in one patient (case 13). An increase in medullary fibrous tissue was the only histopathologic feature evident.

One patient (case 5) had a clinical course which did not conform to the classic picture. Inguinal adenopathy was identified on the left side Feb 16, 1967, and a course of tetracycline was prescribed. Twelve days after the initial examination he was admitted to the hospital, and the nodes were aspirated. Thereafter they gradually reduced in size and

stabilized. Tetracycline therapy was discontinued after the 21st day and treatment with sulfisoxazole was initiated. On March 12, a 4 x 4 cm perirectal abscess developed which required surgical incision. Sulfisoxazole was continued for two complete courses. At the completion of this therapy, the patient was considered cured. Notably, he had remained systemically asymptomatic throughout the entire course.

Comment

The organism responsible for LGV is related to the group of agents which produce psittacosis, ornithosis, trachoma, and inclusion conjunctivitis. The precise method of infection in LGV is unknown. The disease probably spreads during sexual intercourse through contact with infected material from primary lesions, ruptured lymph nodes, or anal discharge.

Lymphogranuloma venereum in the early stages is divided into two syndromes: the inguinal and the genito-anorectal. The inguinal syndrome is characterized by primary genital lesions, ranging from slight erosion to indurated nodules, regional lymphadenopathy, and systemic signs and symptoms. The genito-anorectal syndrome, which accounts for as many as 25 percent of the cases seen in early stages, is seen predominantly in women. This syndrome is characterized by a bloody mucopurulent anal discharge. The anorectal mucosa is edematous hemorrhagic, and friable, with a granular texture to palpation. Adenopathy is not a common finding in this type of LGV. Following the proctitis there may be constipation or diarrhea, tenesmus, and abdominal pain. In the late stages of both syndromes genital elephantiasis, called esthiomene in the female, may occur. In the genito-anorectal syndrome, rectal stricture, fistulae, or perirectal abscesses and other complications may occur.

Lymphogranuloma venereum has an incubation period of one to four weeks in patients in whom the inguinal variety develops. A penile lesion develops in one-third to one-half of the cases. The lesions are relatively painless and last only a few days, which accounts for the small number seen clinically. Most have healed prior to the onset of lymph node enlargement; however, indurated ones may persist for weeks. An occasional primary lesion is found intraurethrally and is accompanied by a thin mucopurulent discharge. Rarely are extragenital lesions seen.

One or two weeks after the primary lesion appears, regional lymphadenopathy develops. The condition, at this stage, may be mistakenly diagnosed as an

TABLE 4. Protein Electrophoresis *

Case No.	Total, gm/100 ml		Globulin, % †			
	Albumin, % †		α_1	α_2	β	γ
6	7.6	45.4	2.8	12.9	12.9	25.9
7	6.7	41.0	5.1	20.5	12.8	20.5
9	7.9	42.4	3.0	9.8	20.5	24.2
12	8.3	43.8	2.6	14.4	8.5	30.7
14	7.7	38.4	3.6	13.8	10.9	33.3
16	7.4	43.1	4.4	13.8	16.1	22.6
17	7.9	37.3	6.2	17.4	11.2	27.9
18	8.2	32.9	4.7	13.5	11.7	37.1

* Normal values are as follows: total, 6.0-8.0 gm/100 ml; albumin, 46.8%-62.7%; α_1 , 1.4%-4.8%; α_2 , 6.7%-14.8%; β , 9.4%-15.8%; and γ , 12.6%-24.6%.

† Values are expressed as percent of total protein.

inguinal hernia. With time, the skin assumes a dusky erythematous or violaceous hue, forms fine wrinkles parallel to the inguinal fold, and may adhere to the underlying nodes. The mass of nodes tends to elongate along the inguinal ligament in a sausage shape. At first the area is nodular and firm. Then some of the nodes soften. In 60 percent to 70 percent of the cases, the nodes rupture to form purulent, draining fistulae. In 20 percent to 25 percent the nodes resolve spontaneously in 8 to 12 weeks, while in 5 percent the nodes develop into chronic indurated inguinal masses. A groove separating the enlarged inguinal and femoral nodes corresponds to the inguinal ligament. This characteristic is almost pathognomonic of LGV.

Systemic signs and symptoms which accompany the inguinal syndrome (more frequently than they accompany the genito-anorectal syndrome), are fever, headache, malaise, arthralgia, meningismus, and conjunctivitis. Skin manifestations include erythema multiforme, erythema nodosum, and scarlatina-form eruptions.

In cases of LGV, laboratory results are neither consistent nor conclusive. Abnormalities include a mild leukocytosis to a WBC of 20,000/cu mm, and relative lymphocytosis or monocytosis. Biologic false positive serologic tests for syphilis occur in 20 percent of the cases. Erythrocyte sedimentation rate is usually elevated, and lipid concentrations are depressed. Reversal of the albumin-globulin ratio occurs.

The Frei skin test and the LGV complement fixation test are the two major diagnostic procedures for LGV. Positive results are not specific for LGV, since the two tests reflect present or past infection by any of the psittacosis group of diseases. In addition, there is no correlation between the skin test reaction or the LGV CF test titer and the clinical severity of the disease.

The Frei skin test produces a positive reaction 12 to 40 days after the primary lesion appears. The LGV CF test, which has proved highly sensitive in 97 percent of known cases of LGV, becomes positive within four weeks after infection. If the Frei skin test reaction is initially negative (a papule less than 6 mm), or the LGV CF test titer is negative (less than 1:10), the tests should be repeated after one to three weeks. Persistent negative results in the presence of disease are rare. Repeat Frei testing will not cause a conversion, and once positive, the test

remains positive for the lifetime of the patient. Conversion of a titer from negative to positive is highly significant in diagnosing LGV. Sigel indicated that a fall in titer can be used as evidence of therapeutic success in the acute stage.

Drug therapy recommended for the treatment of LGV has been one of the sulfonamides, tetracyclines, or both. Chloramphenicol has also been used. Supportive therapy consists of bed rest, cool compresses to involved areas, and aspiration of fluctuant sites.

Therapy is guided by resolution of fluctuant nodes, closing of fistulae, reduction in size of nodes, and response of constitutional symptoms. Laboratory studies may verify the return to normalcy.

Canizares stated that incising nodes was contraindicated because the procedure enhanced elephantiasis, and Koteen reported some studies which indicated that incision prolonged recovery.

In this study 19 of the 20 patients were men, which accounts for the observation of only the inguinal syndrome and only one perirectal abscess. The classic picture described in textbooks, and by Canizares, was observed. The deviations from normal reflected in the findings are consistent with the reports in the literature. The lack of correlation between the Frei skin test and the LGV CF test titer, and the severity of the clinical course of the patient is substantiated. A fall in titer occurred in only two patients during the period of observation and treatment, although therapeutic success was considered accomplished in all patients. A 21-day course of the recommended drugs was used. Only one case was resistant to therapy and required several courses. Both tetracycline and sulfa therapy appeared equally effective in this series. The aspirations and other surgical procedures did not appear to prolong recovery; rather the aspirations prevented rupture of the nodes, minimized complications, and hastened recovery.

Generic and Trade Names of Drugs

Sulfisoxazole—*Gantrisin*.

Chloramphenicol—*Chloromycetin*, *Chloroptic*, *Cylphenicol*, *Mychel*, *Tega-Cetin*.

Tetracycline hydrochloride—*Achromycin V*, *Panmycin Hydrochloride*, *Polycycline Hydrochloride*, *Steclin*, *Tetracyn Hydrochloride*.

(The references may be seen in the original article.)

CURRENT CONCEPTS OF SNAKEBITE TREATMENT

Henry M. Parrish, MD, University of Missouri School of Medicine,
Columbia, Missouri, GP 38(2):79-83, August 1968.

Pit vipers (rattlesnakes, cottonmouths and copperheads) inflict about 99 percent of all venomous snakebites in the U.S. Pit viper venenation (snake venom poisoning) is characterized by puncture wound, pain, edema and erythema. Over 30 percent of bites are accompanied by systemic signs, including shock. All serious pit viper bites should be treated with incision and suction, antivenin, antibiotics and anti-tetanus prophylaxis. Cold therapy can cause excessive tissue necrosis.

Bites by venomous snakes occur frequently in the United States. A recent nationwide survey of this problem indicated that about 6,680 people are bitten annually. However, deaths from snakebites are rare—an average of 14 to 15 a year. This provides a case-fatality rate of less than one-fourth of 1 percent. The very low case-fatality rate reported from this nationwide study results from rather complete reporting of snakebite accidents and deaths, from the fact that many bites by venomous snakes are not life-threatening and from improvements in the clinical management of snakebite.

Venomous Snakes

Only about 10 percent of the species of snakes native to the United States are venomous. Pit vipers of the family Crotalidae make up the vast majority of venomous species. Pit vipers include *Crotalus*, or large rattlesnakes; *Sistrurus*, or small rattlesnakes, and *Ancistrodon*, so-called moccasins—including cottonmouths and copperheads. Coral snakes of the genera *Micrurus* and *Micruroides* are the only other native venomous snakes of medical importance.

At least one venomous snake species is indigenous to every state in the United States except Maine, Alaska and Hawaii. Table 1 lists the venomous snakes found in each state and the District of Columbia. One or more species of large rattlesnakes (*Crotalus* sp.) are found in every state except Maine, Michigan, Delaware, the District of Columbia, Alaska and Hawaii. Small rattlesnakes (*Sistrurus* sp.) are found in 26 states. Cottonmouths are indigenous to 16 states located in the southeastern and southwestern parts of the country. Copperheads are found in 29 states (and the District of Columbia) in the eastern two-thirds of the United States. Coral

snakes are native to 11 states located in the southeastern and southwestern parts of the country.

Epidemiologic Pattern

Snakebites result from an interaction of the biologic characteristics of snakes, human activities and environmental circumstances. States having the highest bite rates per 100,000 population are North Carolina, Arkansas, Texas, Georgia, West Virginia, Mississippi, Louisiana and Oklahoma. Males are bitten more frequently than females and persons 10 to 19 and 5 to 9 years of age show a high incidence of bites. Ninety-four percent of bites occur from April through October, with July and August the peak months. These months coincide with the time when snakes are most active and when people have greater exposure from outdoor occupations and recreation. Most bites are inflicted between 6:00 a.m. and 8:59 p.m. even though some venomous snakes are nocturnal feeders.

Clinical Diagnosis

It is essential to make a distinction between a poisonous snakebite and venenation (snake venom poisoning). This is important because it is possible for a poisonous snake to bite someone without injecting enough venom to produce venenation. This is the case in about 25 percent of bites by venomous snakes in the United States. Fortunately, the signs and symptoms of venenation by North American pit vipers (rattlesnakes, copperheads and cottonmouths) are quite similar.

Pit viper venenation is diagnosed primarily by local signs and symptoms. Systemic manifestations usually are found only in more serious cases of venenation and their onset may be delayed for several hours.

The local signs and symptoms of pit viper venenation are the two "P's" (puncture wound and pain) and the two "E's" (edema and erythema). In most cases, at least three of the four signs are present. One or more fang puncture wounds are necessary to produce snake venom poisoning. Superficial lacerations from fangs usually do not result in venenation. Tooth marks, other than fang punctures, may or may not be present. Pain in or around the puncture wound occurs in about 95 percent of pit

TABLE 1. *Venomous Snakes Found in Various States and the District of Columbia*

Region and state	Large rattlesnake	Small rattlesnake	Cotton-mouth	Copper-head	Coral snake
NEW ENGLAND					
Maine	—	—	—	—	—
New Hampshire	X	—	—	—	—
Vermont	X	—	—	—	—
Massachusetts	X	—	—	X	—
Rhode Island	X	—	—	X	—
Connecticut	X	—	—	X	—
MIDDLE ATLANTIC					
New York	X	X	—	X	—
New Jersey	X	—	—	X	—
Pennsylvania	X	X	—	X	—
EAST NORTH CENTRAL					
Ohio	X	X	—	X	—
Indiana	X	X	—	X	—
Illinois	X	X	X	X	—
Michigan	—	X	—	—	—
Wisconsin	X	X	—	—	—
WEST NORTH CENTRAL					
Minnesota	X	X	—	—	—
Iowa	X	X	—	X	—
Missouri	X	X	X	X	—
North Dakota	X	—	—	—	—
South Dakota	X	—	—	—	—
Nebraska	X	X	—	X	—
Kansas	X	X	X	X	—
SOUTH ATLANTIC					
Florida	X	X	X	X	X
Georgia	X	X	X	X	X
South Carolina	X	X	X	X	X
North Carolina	X	X	X	X	X
Virginia	X	—	X	X	—
West Virginia	X	—	—	X	—
Maryland	X	—	—	X	—
Delaware	—	—	—	X	—
District of Columbia	—	—	—	X	—
EAST SOUTH CENTRAL					
Tennessee	X	X	X	X	—
Kentucky	X	—	X	X	—
Alabama	X	X	X	X	X
Mississippi	X	X	X	X	X
WEST SOUTH CENTRAL					
Arkansas	X	X	X	X	X
Louisiana	X	X	X	X	X
Oklahoma	X	X	X	X	—
Texas	X	X	X	X	X
MOUNTAIN					
Montana	X	—	—	—	—
Idaho	X	—	—	—	—
Wyoming	X	—	—	—	—
Colorado	X	X	—	—	—
New Mexico	X	X	—	—	X
Arizona	X	X	—	—	X
Utah	X	—	—	—	—
Nevada	X	—	—	—	—
PACIFIC					
Washington	X	—	—	—	—
Oregon	X	—	—	—	—
California	X	—	—	—	—
Alaska	—	—	—	—	—
Hawaii	—	—	—	—	—

viper venenations. This pain has been described as sharp and burning and it usually develops within five minutes after the venom is injected. Pain tends to become more severe as the venom spreads throughout the tissues.

Edema and erythema are always present in pit viper venenation. The swelling and erythema begin around the fang punctures and develop within about 30 minutes. These signs of venenation extend as the venom spreads. The edema may continue to

spread for 12 to 24 hours. Ecchymoses and hemorrhagic blebs may develop around the puncture sites after several hours. If local edema and erythema have not occurred within four hours after a snakebite, one can safely conclude that the patient does not have pit viper venenation.

Systemic signs and symptoms include shock; nausea; vomiting; diarrhea; melena; numbness, tingling and paresthesias in the extremities or around the mouth; muscular fasciculations in the bitten extremity; coma; convulsions, and motor or respiratory paralysis. Anemia and alterations of the coagulation mechanism may occur.

The severity of venenations may be classified as follows:

Grade 0—no venenation: Fang or tooth marks, minimal pain, less than 1 in. of surrounding edema and erythema; usually no systemic involvement.

Grade 1—minimal venenation: Fang or tooth marks, severe pain, 1 to 5 in. of surrounding edema and erythema in first 12 hours after bite; usually no systemic involvement.

Grade 2—moderate venenation: Fang or tooth marks, severe pain, 6 to 12 in. of surrounding edema and erythema in first 12 hours after bite; systemic involvement sometimes present (nausea, vomiting, giddiness, shock or neurotoxic symptoms).

Grade 3—severe venenation: Fang or tooth marks, severe pain, more than 12 in. of surrounding edema and erythema in first 12 hours after bite; systemic involvement usually present.

In the nationwide survey of venomous snakebites, 27 percent were classified as grade 0 (no venenation); 37 percent were grade 1 (minimal venenation); 22 percent were grade 2 (moderate venenation), and 14 percent were grade 3 (severe venenation). Thus 64 percent of the bites (grade 0 and grade 1) were not life-threatening. This finding should reassure physicians who treat snakebites. Nevertheless, it should not stop bite victims from promptly seeking medical care.

Treatment

Since pit vipers (rattlesnakes, cottonmouths and copperheads) inflict about 99 percent of all venomous snakebites in this country, the discussion of treatment will be confined to pit viper bites.

A tourniquet should be applied lightly to the involved extremity several inches above the bite. The constricting band should be only tight enough to occlude the superficial venous and lymphatic flow. It should not occlude the arterial circulation and it should be released every 10 to 15 minutes for a

minute or two. As edema resulting from venom poisoning spreads, the tourniquet should be advanced to keep just ahead of the swelling. The purpose of the tourniquet is to impede the spread of venom until incision and suction can be used to remove the venom mechanically or until polyvalent crotaline antivenin can be administered to neutralize the venom.

Incision and suction removes venom from experimental animals up to about 120 minutes after the venom is injected. The sooner this measure is started, the larger the amount of venom that can be removed. Suction should be continued for about one hour. Incisions, $\frac{1}{4}$ in. long and $\frac{1}{8}$ to $\frac{1}{4}$ in. deep, are made into the subcutaneous tissues over the fang punctures. Immobilization aids in limiting the spread of venom. However, if one must decide between immobilization and seeking prompt medical treatment, the latter should be chosen.

In addition to incision and suction, the three "A's" (antivenin, antibiotics and antitetanus prophylaxis) are recommended for all serious pit viper bites. Antivenin manufactured in this country will neutralize the venoms of all North American pit vipers. Since antivenin is produced from horse serum, the patient should receive a skin test before antivenin is given. Antivenin diluted in 500 ml. of normal saline may be given intravenously. Radioisotope studies have shown that antivenin accumulates at the site of the wound more rapidly after intravenous injection than after intramuscular administration. Although antivenin has been given intravenously for several decades in other countries, this route was not used frequently in the United States before 1960. Injection into the local bite area is not a particularly effective way to administer antivenin.

I have found the following amounts of antivenin useful in treating the various grades of venenation: grade 0 (no venenation) requires no antivenin; grade 1 (minimal venenation) may require 10 ml. (one ampule) of antivenin; grade 2 (moderate venenation) requires 30 to 40 ml. and grade 3 (severe venenation) requires 50 ml. or more. Serum sickness develops in a high proportion of patients who have received large doses of antivenin.

Since snakes' mouths and venoms may harbor pathogenic organisms, antibiotics and tetanus toxoid or tetanus immune globulin should be administered prophylactically. Because gram-negative organisms are predominant, a broad-spectrum antibiotic is indicated.

Corticosteroids and corticotropin (ACTH) do not affect the survival rate of animals poisoned with

pit viper venoms. They probably should not be used during the first few days after venenation, although they may be beneficial later in treating serum sickness resulting from antivenin therapy.

Antihistamines are contraindicated since they shorten the survival time of animals poisoned with pit viper venoms. Shock resulting from venom poisoning should be treated with infusions of blood,

plasma, saline solution and vasopressor drugs. Analgesics are needed to relieve pain.

Recently there have been reports of excessive tissue necrosis and amputations associated with cold therapy, such as packing an extremity in ice or using ethyl chloride. In my opinion, cold therapy should not be used in treating pit viper bites.

(The figure may be seen in the original article.)

MEDICAL ABSTRACTS

LOW BACK PAIN: PATHOMECHANICS AND A REGIMEN OF TREATMENT

*Nancy C. Kester, MD, Arch Phys Med 49(7):
396-402, July 1968.*

The incidence of low back derangement is great and appears to be increasing. Greater success in the treatment of low back pain can be achieved by the physician who understands the anatomic and pathomechanical principles of the low back and applies these principles properly in treatment of low back pain. From a mechanical point of view, pain in the low back is the result of dysfunction of the spine either in its static or kinetic state. Rest, proper positioning, traction and heat are indicated in the treatment of the acutely painful back. When the symptoms subside to the subacute or chronic phase, the back must be reconditioned by properly supervised exercises. The basis for proper exercises for the majority of deranged low backs is the pelvic tilt with flattening of the lumbar lordosis. The exercises must also provide for isometric strengthening of back extensors, strengthening of abdominal muscles, eliminating contractures of hip flexors, and stretching of tight hamstring muscles.

CARDIOVASCULAR SCREENING TO ASSESS RISK OF CORONARY HEART DISEASE

*J. T. Doyle, MD, S. H. Kinch, MS, and D. F. Brown,
MD, Public Health Rep 83(8):659-667,
Aug 1968.*

During an 18-month period, February 1965 through mid-July 1966, 8,512 male and female employees of the New York State Department of Civil Service in Albany were seen in a cardiovascular screening program. Twenty-nine persons had electrocardiographic evidence of myocardial infarction, and

32 were diagnosed as having hypertensive heart disease.

Observations on the total serum cholesterol concentration, arterial blood pressure, body weight, and smoking habits were generally similar to those reported from other studies.

Estimation of prevalence of selected risk factors indicated that cigarette smoking is the most common. Fewer than 1 percent of the total group exhibited elevations of total serum cholesterol concentration, arterial blood pressure, and heavy cigarette smoking in combination.

Data useful in the assessment of the cardiovascular and risk factor status of large groups can be obtained relatively easily and inexpensively through screening programs. Such information is essential for the identification of individuals who may be eligible for programs designed to mitigate risk factors as well as for the evaluation of such efforts. A considerable number of persons will apparently support such programs and are, based on this experience, willing to participate in more extensive examination procedures.

STRABISMUS

*Gunter K. von Noorden, MD, Arch Ophthalmol
80(3):384-402, Sept 1968.*

This review covers virtually all publications, during 1967, related to strabismus that are of more than passing clinical or fundamental interest and were available to the reviewer. Editorial restrictions limiting this discussion to approximately 100 publications made it necessary to be selective and to omit some published papers. Since not all 1967 issues of the foreign journals had arrived by the time this review was prepared for publication, any articles related to

strabismus in those publications will be considered in next year's review.

The following classification was found useful in organizing the material:

- Books, journals, meetings
- Basic sciences
 - Anatomy, physiology, pathophysiology Electromyography
- Heredity
- Types of strabismus
- Diagnosis
- Sensory adaptations
 - Suppression
 - Amblyopia
 - Anomalous retinal correspondence (ARC)
- Nonsurgical treatment
 - Miotics
 - Orthoptics-Pleoptics
 - Glasses
- Surgical Treatment
 - Horizontal muscles
 - Vertical and oblique muscles
 - A and V patterns
 - Complications
 - Miscellaneous subjects

HOST DETERMINANTS OF RESPONSE TO ANTIMICROBIAL AGENTS

*L. Weinstein, PhD MD, and A. C. Dalton, MD,
New Eng J Med 279(9):467-473, Aug 29, 1968
and 279(11):580-588, Sept 12, 1968.*

The enthusiasm for definition of the etiology of an infection and for selection of the most effective anti-

microbial agent often leads to inadequate consideration of the host, the battleground for the clash between the invading organism and the anti-infective compound. The emphasis is placed on the "bug" and the "drug," and little or no attention paid to what may be an important role of factors operating in the patient, other than those directly related to the infectious process, in conditioning the response to therapy. Although the infection itself determines to a great degree the kind of treatment to be employed, innate host factors, completely unrelated to the acute disorder, are often the prime determinants not only of the type of antibiotic selected but also of its dose, route of administration, risk and nature of untoward effects and therapeutic effectiveness. Experience has taught that the highest level of success in the treatment of infections or any other kind of disease is most likely to be achieved when three factors—the injurious agent, the drug used to combat it, and the patient being treated—are considered.

The purpose of this paper is to review and analyze some of the published data as well as personal observations that indicate that particular host factors are of great consequence in determining the outcome of the treatment of infection. Among these are age, pregnancy, genetic background, renal and hepatic function, electrolyte balance, nervous-system abnormalities, metabolic disorders, indigenous microbial flora, allergy and defense mechanisms.

DENTAL SECTION

EVALUATION OF THE NAVY PLAQUE INDEX

CDR John M. Smith, DC USN.

The teeth of twenty-two patients were stained with a commercial erythrosine disclosing solution according to the manufacturer's directions. Each tooth was scored according to the criteria of the Navy Plaque Index (NPI) and a comparison was made between the median scores obtained utilizing the NPI and the median scores obtained utilizing

the Navy Plaque Index (simplified) (NPI(S)). The NPI(S) scores only six selected teeth, (#3, 9, 12, 19, 25, and 28), by the same method used for scoring the entire dentition with the NPI.

A close correlation was found to exist between these scores, indicating that the teeth used in the NPI(S) serve as accurately as the entire dentition when evaluating incidence of plaque in a group. The highest individual tooth scores occurred on the selected teeth 45.4 percent of the time, somewhat limiting the usefulness of these teeth for individual patient evaluation. The range of individual tooth scores was from 0 to 22 and the average high score was 17.2.

The opinions and assertions contained herein are those of the author and are not to be construed as reflecting the views of the Navy Department or the Naval Service at large.

It was concluded that the NPI(S) will give a true picture of the group and will provide a useful impression of an individual's oral hygiene status and, therefore, appears adequate for use in a screening-type examination.

(Abstract of a report submitted during Postdoctoral Fellowship training.)

PHOTOSENSITIVE DERMATITIS FROM SOAPS

A. E. Ison and J. B. Tucker, Dent Abs 13(9):549, Sept 1968.

Antibacterial soaps containing halogenated salicylanilides (of the type recently added to soaps in the United States as antimicrobial agents) cause photosensitive skin eruptions that can be reproduced by a simplified photopatch testing technic.

Twelve patients with photosensitive reactions due to soaps had positive tests to either dibromosalicylanilide or tribromosalicylanilide, or to a soap

solution containing these substances, but tests were negative if soap solutions free of halogenated salicylanilides were used. Of 21 patients with other dermatologic disease, only 1 had a positive test to halogenated salicylanilides.

The 12 patients with photosensitive eruptions had histories of having used Safeguard, Lifebuoy, or Zest soaps. The dermatitis improved when these soaps were eliminated. In two patients inadvertent use of a soap containing halogenated salicylanilide produced a flare-up of the dermatitis.

Recent studies in animals indicate the mechanism leading to the production of photosensitive reactions with tribromosalicylanilide may be allergic. However, the mechanism of many of the other known photosensitizers is toxic, not allergic.

(A. E. Ison and J. B. Tucker, 1600 Northwest 10th Avenue, Miami, Fla. 33136. Photosensitive dermatitis from soaps. *New Eng J Med* 278:81-84, Jan 11, 1968. Copyright by the American Dental Association. Reprinted by permission.)

PERSONNEL AND PROFESSIONAL NOTES

MARINE HEADQUARTERS STAFF BRIEFED ON NAVAL DENTAL CORPS' ROLE IN REHABILITATING WOUNDED MARINES

Naval Dental School, NNMCMC, Bethesda, Md.—The Naval Dental Corps recently presented a briefing to staff officers and civilians from Marine Corps Headquarters on the latest developments in some unusual and little-known types of care which Navy dentists provide for Marines.

Few are aware of the Naval Dental Corps' responsibility for rehabilitating sailors and marines with disabling and disfiguring wounds of the face, jaws, and eyes, sustained in combat or in accidents. This role was the subject of the briefing.

The first speaker was CAPT Philip J. Boyne, DC USN, Director of the Dental Research Department at the Naval Medical Research Institute, Bethesda. A leader in the field of bone biology and transplantation techniques, CAPT Boyne is also the father of a young marine now stationed in Okinawa. He described the use of porous tubing for better regeneration of severed facial nerves, and the use of metal cribs to confine the transplanted bone chips which stimulate the growth of new bone and mold it to the desired shape.

Next, CAPT Howard B. Marble, DC USN, Head of the Oral Surgery Department of the Naval Dental

School, showed how oral surgeons repair shattering facial wounds sustained by marines in combat. He also demonstrated dramatic results obtained in correcting those hereditary defects that either prevent a patient from eating properly or cause severe psychological problems because of the patient's appearance.

Providing ocular prostheses for patients who have lost eyes is a more unusual responsibility of the Navy's Dental Corps. CDR David N. Firtell, DC USN, Head of the Naval Dental School's Maxillofacial Prosthetics Division, reviewed progress in this area of rehabilitation.

In addition to providing custom-fitted artificial eyes for patients, naval dental officers have teamed with their eye surgeon colleagues to design better prosthetic implants. The permanent surgical implant, which is inserted when the damaged eye is removed, helps maintain the function of eye muscles and improves the appearance, movement, and comfort of the artificial eye.

Among those attending the briefing was MGEN Louis I. Metzger, USMC, Deputy Chief of Staff, Research, Development, and Studies.

The featured speakers were introduced by CAPT William E. Ludwick, DC USN, Staff Dental Officer,

Headquarters Marine Corps, and CAPT William C. Wohlfarth, DC USN, Commanding Officer, Naval Dental School, National Naval Medical Center, Bethesda, Maryland.

GUAM DENTAL STUDY GROUP

The recently reorganized Guam Dental Study Club held its first meeting at the Top O' the Mar, Commissioned Officers' Mess, Nimitz Hill, Naval Station, Guam, on 9 October 1968. Lt R. P. Masella, DC USN, of the U.S. Naval Dental Clinic, Guam, presented a paper entitled, "Complete and Partial Traumatic Displacement of Teeth." Ensuing programs will present topics designed to promote professional growth and intellectual stimulation as well as topics of general information. The club plans to meet the second Wednesday of each month.

The Guam Study Club is composed of twenty-four Naval Dental Officers, eleven Air Force Officers, one Public Health Dental Officer and nine civilian dentists. CAPT Harry C. Pund, Jr., DC USN, U.S. Naval Dental Clinic, Guam, is the president for 1968-69 and CAPT E. J. Martin, DC USAF, 863rd Medical Group, Andersen Air Force Base is the secretary.

NAVAL DENTAL CORPS CONTINUING EDUCATION PROGRAM

A change in the schedule of Continuing Education Courses as presented in the U.S. Navy Medical News Letter, Volume 52, No. 4 at the Naval Dental Center, San Diego, California, during the Fiscal Year 1969 is as follows:

Preventive Dentistry vice
Removal Partial Dentures
7-11 April 1969

Two Continuing Education Courses listed in the Journal of American Dental Association 77(3): 658-659, September 1968 are similarly affected as follows:

Delete:

Removable	U.S. Navy, 11th Dist.	Apr 7-11
Partial	San Diego	
Dentures		

Change date to:

Preventive	U.S. Navy 11th Dist.	Apr 7-11 vice
Dentistry	San Diego	Sept 16-20

NURSE CORPS SECTION

PEDIATRIC CONFERENCE

The Nursing Division, Bureau of Medicine and Surgery, Navy Department, sponsored a pediatric conference for Nurse Corps Officers at the Naval Medical School, National Naval Medical Center, Bethesda, Maryland, from 28 October through 1 November 1968. Sixteen Navy Nurse Corps Officers attended, representing fifteen Naval Hospitals.

One of the outstanding highlights in the conference was an afternoon seminar on Child Growth and Development. This seminar was presented by Mrs. B. Quincy Haynes, R.N., Associate Director and Nurse Consultant, Medical and Scientific Department, United Cerebral Palsy Association, Inc., New York, New York. Mrs. Haynes lectured on the topic and using a doll, demonstrated ways of determining age and detecting abnormalities in growth and development by observation and touch. Then, to everyone's delight, five small babies, ranging in age from 9 weeks to 9 months, arrived. The participants were

divided into small groups and each had the opportunity to examine a baby.

After completing the examination, an informal discussion was held with a representative from each group reporting the findings. Amazingly, each group came very close to determining the correct age of the babies.

The next conference planned for active duty Navy Nurse Corps Officers will be on the subject of Communicable Disease. It is scheduled for the week of 18 November 1968 at the Naval Medical School.

A STUDY OF PATIENT ATTITUDES TOWARD OLDER PEOPLE

The following is an abstract of a thesis submitted by LCDR Shirley E. Merrill, NC USN in partial fulfillment of the requirements for the degree of Master of Nursing at the University of Washington.

The purpose of this study was to obtain information regarding attitudes towards older people and

satisfaction with roommate assignment among the various age groups who were paired with older patients in a hospital setting. All one hundred respondents were hospitalized in double (two bed) rooms and were either over sixty-five years of age or were roommates of older persons. The respondents completed the Tuckman and Lorge "Attitudes Toward Old People"¹ scale and a biographical data sheet stating their preference for age of a roommate, their satisfaction with room assignment, their morale, sex, and educational background.

Statistical analysis, by the one- or two-way analysis of variance, revealed the following data to be significant: (1) respondents sixty-five years of age and older had more stereotyped responses towards old people than did either the young or middle-aged groups, (2) female respondents stereotyped old people more than male respondents, (3) those respondents over sixty-five years of age with only a grade school education had more stereotyped attitudes towards old people than did those with either

a high school or college background, (4) the roommates of respondents over sixty-five who stated their morale as low had more stereotyped responses than did the roommates of those old patients who stated their morale as medium or high, and (5) more of the respondents over sixty-five years of age preferred roommates under sixty-five.

Ninety-one percent of the respondents stated that their roommates affected their satisfaction with their room placement; 52 percent stated their roommates in some way affected their morale. In view of these findings, it appears that a more thoughtful and systematic approach should be given to the placement of geriatric patients within the hospital setting.

The complete thesis is available to interested persons by applying to Code 324, Nursing Division. We plan to occasionally publish selected abstracts of studies done by Nurse Corps officers.

¹Jacob Tuckman and Irving Lorge, "Attitudes Toward Old People," *The Journal of Social Psychology* 37:249-260, May 1953.

AEROSPACE MEDICINE SECTION

NEWS OF PERSONNEL

On 1 October 1968 CAPT Roland A. Bosee, MSC USN retired from the Navy after more than 28 years of active duty. Upon entering the Navy in June 1940, CAPT Bosee completed flight training and was designated a Naval Aviator. For the next seven years he served in a number of aviation billets aboard carriers and aircraft squadrons. He spent two and one-half years aboard carriers during World War II and participated in many South Pacific operations. From January 1947 until September 1947 he was Air Group Commander of Air Group 67. In that same year he reported to the Naval Air Test Center, Patuxent River, Maryland, and shortly thereafter transferred to the newly established Medical Service Corps of the U.S. Navy. Since that time he has been involved as an Aerospace Physiologist and Naval Aviator in Research and Development, primarily in the area of biomedical engineering. CAPT Bosee played a major role in developing the Navy full pressure suit and the modifications to the suit, resulting in its use by the Project Mercury astronauts. He was involved in the development and flight evaluation of many items of pilot and safety equipment. These included protective helmets, pressure breathing oxygen equipment, automatic para-

chute release systems and the integrated parachute harness system. While assigned as the Test Director, Naval Parachute Facility, El Centro, California, CAPT Bosee participated in many parachute jumps and ejection seat tests to operationally assure himself of the suitability and reliability of new approaches and concepts of escape systems. For the past four years CAPT Bosee has been Director, Crew Systems Division, Naval Air Systems Command, with additional duty in the Bureau of Medicine and Surgery as Head, Aerospace Medicine Equipment Branch. CAPT Bosee has been the recipient of a number of honors and awards, including election to the International Academy of Aviation Medicine, the Special Aerospace Medicine Honor Citation from the American Medical Association, and the Harry G. Moseley award from the Aerospace Medical Association for significant contributions to flight safety. He is a Fellow in Aerospace Medicine and an Associate Fellow of the American Institute of Aeronautics and Astronautics. Upon his retirement CAPT Bosee was awarded the Legion of Merit for his outstanding contribution to naval aviation. CAPT Bosee has assumed the position of Director of the Philadelphia General Hospital Research Fund and Director of Research Activities.

CAPT Roger G. Ireland, MC USN has relieved CAPT Bosee as Director, Crew Systems Division, Naval Air Systems Command. He formerly served as Director, Aerospace Crew Equipment Department, Naval Air Development Center. CAPT Ireland has wide operational experience, as well as experience in the field of testing and evaluation of flight equipment, and is well qualified to move into this new position.

CAPT W. L. Goldenrath, MSC USN assumed the position as Director, Aerospace Crew Equipment Department, Naval Air Development Center in September. He succeeded CAPT Roger G. Ireland, MC USN. CAPT Goldenrath had reported to the Aerospace Crew Equipment Department as Deputy Director from the Aviation Physiology Training Unit, Naval Air Station, Miramar, California. In addition to being the Senior Aerospace Physiologist at the APTU, CAPT Goldenrath performed additional duty as Personnel Survival Equipment Officer on the staff of Commander, Naval Air Force, Pacific Fleet based in San Diego, California.

On 16 July 1968 another Naval Flight Surgeon received a designation of Naval Aviator. LCDR Donald E. Sampson, MC USN, after serving as a Flight Surgeon with Marine Fighter Attack Squadron 322 at DaNang and Chu Lai, for a year, flying in the F-4B and as Medical Officer on helicopter medical evac flights, returned to Pensacola for basic flight training. He completed advance training at Corpus Christi, Texas. In the same ceremony in which Doctor Sampson received his wings, he also donned his Lieutenant Commander shoulder boards. For his service in Vietnam, LCDR Sampson was awarded three air medals and the Navy commendation medal with combat "V" in addition to the area service medals. LCDR Sampson is presently serving as Flight Surgeon to Attack Squadron 174 at Naval Air Station, Cecil Field, Florida where he is flying the A-7 Corsair II.—AeroMed, BuMed.

SUBMISSION OF SF'S 88 AND SF'S 89 ON CREWMEMBERS AND NONCREWMEMBERS

The record officer at this BUREAU continues to receive several hundred Standard Forms 88 each week on crewmembers and noncrewmembers. Page change 43 of the Manual of the Medical Department discontinued the requirement for the submission of these physical examinations except in cases requiring a waiver or when a BUMED decision is desired. In the interest of reducing the workload on an already overtaxed division, compliance with MAN-

MED, art. 15-69(8)(d) is earnestly recommended.
—AeroMed, BuMed.

FLIGHT EQUIPMENT

Several months ago an Army helicopter pilot assigned to a med-evac unit of the First Cavalry Division (Airmobile), stationed in Vietnam, requested the Crew Systems Division, Naval Air Systems Command, for some items of Navy flight equipment. Following receipt of the items and after using them for a period of time, he wrote an informal letter to the Director, Crew Systems Division. The following are excerpts from that letter:

"I would like at this time to thank you for the very fine equipment that you have forwarded to me. I have already had a chance to use the PRC-90 radio to effect the rescue of one of our med-evac pilots. I had loaned the pilot the radio for his use during a hot mission that took place in the Ashau Valley. This pilot and his crew were shot down during the attempted rescue of wounded American soldiers. The aircraft crash-landed in dense jungle. There were several badly wounded crew members aboard the aircraft. When the aircraft went in, there was no accurate report of his position. After the aircraft was on the ground, the pilot was able to establish radio contact with friendly units with the PRC-90. Through the use of this very fine piece of equipment the whole crew was rescued without the loss of one life. I am sorry to say, but this is the only survival radio in my unit. I share this radio with my fellow pilots, whoever is flying the No. 1 position uses the PRC-90 as the No. 1 crew is the most likely to be hit by enemy ground fire.

"The Nomex flight suit is a very fine suit, I have found only one fault in the design of it. The method of taking up the slack in the pants cuff should be replaced with a zipper, much like the old style flights had. This is the only flaw that has shown up in the suit since I have been wearing it.

"The Nomex flight gloves are a great improvement over the old leather style gloves, in that they are much more comfortable to the wearer. I feel that the one drawback will be in the area of glove life. I feel that they will wear out rather quickly. The problem will be in the area of stitching where the Nomex material is joined with the leather portion of the glove. I will forward a more comprehensive report to you at a later date.

"Well, sir, I will close for now, but in closing I would like to thank you from the bottom of my heart for all you have done for me. I will be in touch with

you again with a comprehensive report on the equipment you sent me."

Editor's Note: Personnel in the Crew Systems Division, Naval Air Systems Command and their field laboratories are doing a very fine job in developing new flight equipment and updating old for our Navy/Marine Corps aircrew personnel. They are sincerely interested in making such equipment the finest available. Constructive comments and criticisms from our flight surgeons in the field, directly to the Crew Systems Division or to the Aerospace Medicine Technical Division (Code 52), Bureau of Medicine and Surgery, regarding flight equipment are greatly encouraged. Any other informative material from our people in the field, which is appropriate for circulation through the Aerospace Medicine Section of the U.S. Navy Medical News Letter, is also encouraged. Please submit such material to Director, Aerospace Medical Technical Division (Code 52), Bureau of Medicine and Surgery, Washington, D.C. 20390.)

MISSING SURVIVAL EQUIPMENT

A safety council has reported in its minutes that CO₂ cylinders have been found to be missing from life vests in aircraft. "This appears to be a repeat of an old problem concerning the disappearance of various pieces of survival equipment," the minutes state. "In the past, CO₂ bottles, one cell flashlights and signal flares have been discovered missing." Grave consequences could result from the misuse of this survival equipment or the unauthorized removal of any part of it, the council pointed out.

Life vests and other flotation equipment are routinely checked by aircrew survival equipment maintenance men every 90 days. Determination of the condition of the life vest is the responsibility of the wearer (BacSep 55-61 refers). However, anyone who tampers with survival equipment or takes a CO₂ cylinder from a life vest is indirectly responsible if injury or death in a survival situation results. Commanding Officers should insure that their men are fully aware that tampering with survival equipment can cost someone his life.

Editor's Note: Squadron Flight Surgeons have a vested interest in this area and should be on the constant alert to prevent unauthorized use and tampering with safety and survival equipment.—AeroMed, BuMed.

"TRIP TO WHERE"

This Trip Isn't Necessary. Some adventurous types might be tempted to try LSD—just once, just to see what it's like.

Our advice is *don't!* Here's why:

A "trip" lasts from six to twelve hours but can last for weeks, even months. A small dose of LSD has been known to induce severe psychotic reactions, including hallucinations and acute panic with suicidal and homicidal states. But more insidious, perhaps, is the "flashback", a recurrence of the psychotic reaction after a single use, weeks, months or even years later. While there's still a lot to be learned about this drug, there is evidence of other serious changes in body chemistry.

Known users of LSD in the Air Force are to be:

1. Grounded—disqualified for flying.
2. Disqualified for air traffic control duties.
3. Disqualified for duties under the Human Reliability program.

Furthermore, use of LSD resulting in a disabling condition could possibly lead to separation from military service with loss of all medical rights after discharge.

Don't be lulled into trying this stuff. The experts know beyond any doubt that LSD is extremely dangerous and very unpredictable.—Aerospace Safety Magazine, Norton Air Force Base, Calif.

Editor's Note: The above article appeared in a recent issue of the Air Force Aerospace Safety Magazine. Its message is appropriate for inclusion by the Flight Surgeon in his lectures to "All Pilots" and "All Hands". The advice is as applicable to narcotics, marijuana and other dangerous drugs as it is to LSD. In order to properly advise personnel, a review of SECNAV Instruction 6710.1, 25 April 1968, and BUPERS Instruction 5510.11A, 24 February 1964, is recommended. In addition, the films MN 10507, "LSD" and MN 10494, "Trip to Where" should be freely shown. Both of these films were produced by the Navy and are excellent. "LSD"—a 30-minute color film presents LCDR Walt Minor, MC USN, discussing the perils of LSD and its known effects. It is a standup lecture film expertly presented. "Trip to Where"—a dramatic 50-minute color presentation dwells on all aspects of drug abuse with particular stress on the impact of LSD and the consequences of its use, illustrated by the experiences of three seamen. "Trip to Where" is of special interest to civilian audiences in the 14 to 30 year age group and has been released for non-profit civilian showing.

CRUISE REPORT FROM WESTPAC

Cruise reports received in the Bureau of Medicine and Surgery from our carriers upon their return to

CONUS from a deployment are sources of valuable information and helpful recommendations. The following material was excerpted from the report of a CVS upon completion of a WestPac Cruise:

I. Pre-Deployment

The chest X-ray program should be conducted several months prior to deployment. The nearer the deployment date the more people there are on leave making it difficult to obtain 100% participation.

Immunizations should be started several months prior to departure. Cholera, second plague and gamma globulin can be administered while enroute to WestPac.

A vigorous program of educating personnel who wear eyeglasses of the need for two pair of spectacles should be conducted several months prior to departure date.

II. Logistics and Supply

No great problems were experienced in obtaining the more commonly used medical supplies in WestPac. Pearl Harbor is an excellent place to "Top Off" your supplies prior to sailing for WestPac. Subic was well stocked and has an excellent ServMart. Yokosuka was well stocked. The supply ships were also a good source of supply while at sea. Ships visiting Singapore should not plan on drawing routine supplies from the British. Emergency items could probably be procured but only on a very limited basis.

A careful survey of the Medical Department should be made prior to deployment to insure that spare parts which may be needed are on board. Frequently these may not be obtainable anywhere in WestPac.

The MSC officer can turn in any requisitions you may have upon his early arrival in each port. This also helps to ensure that the supplies needed will be received prior to departure and makes "Walking Through" requisitions unnecessary.

A good variety and supply of insecticides should be on board prior to deployment. Difficulty was encountered in obtaining 5% DDT in oil until Yokosuka was finally able to provide us with some.

III. Medical facilities at ports visited

Pearl Harbor, Hawaii. The Navy Administrative Unit at Tripler Army Hospital will render assistance in arranging appointments at the various clinics of the hospital. The Dispensary at Pearl Harbor will also be able to assist you with special problems.

Subic Bay, R. P. The Naval Hospital at Subic has most specialty clinics available. Arrangements may be made through the Naval Hospital for appointments in the remaining clinics at Clarke Air Force Base.

Yokosuka, Japan. The Naval Hospital at Yokosuka, has all clinics available. They will take the Medical Guard if you so desire.

Hong Kong, B. C. C. A Medical Guard was maintained by YORKTOWN while at Hong Kong. Hospital Corpsmen were assigned to Shore Patrol. The British Military Hospital is available for emergencies.

Singapore. The Royal Navy Sick Quarters at HMS TERROR is manned 24 hours daily. Ambulance service is available. The British Military Hospital is available for emergencies and is located about 15 miles from the dockyard. Sickcall was held daily aboard YORKTOWN while at Singapore.

It is recommended the MSC officer be sent into port a few days before arrival of the ship to arrange consults as necessary. The hospitals appreciate this advance notice and it helps to assure all patients requiring consultation will be seen during the inport period.

IV. Miscellaneous Comments

Because of the PUEBLO incident this carrier was deployed to the Sea of Japan for an unexpected lengthy tour. Exposure of personnel to cold temperatures, combined with strong winds, became a concern to the Medical Department. Plan of the Day notes were published advising the crew of the dangers and symptoms of frostbite. Inspections of the lookouts were made by Medical Department personnel to insure that they were adequately dressed to withstand the elements. Brandy and whisky were prescribed as required for personnel coming off watch.

Helicopters flying plane guard were equipped with a new body bag lined with several blankets. In the event a pickup was made it was felt that this would aid in keeping a patient warm until return to the ship. The body bag is impervious to water and provides excellent protection against the wind. The parachute loft provided a carrying case for these bags with a separate pouch for a unit one first aid bag.

Close liaison should be maintained with air operations to assure minimal delays in the transferring of patients.—AeroMed, BuMed.

CIRCADIAN RHYTHM

Whether it be referred to as built in "physiological clock" or a "day/night metabolic cycle," it is well established that each individual has a personal peak performance period. During the 24 hour day, he goes through a work/rest cycle in which very definite changes take place in his bodily activity. Body temperature, blood pressure, respiration, and oxygen consumption subside during the "nighttime" part of the cycle. While the sympathetic nervous system (the system that "turns you on") prevails during the "daytime" for liberation of more energy, the parasympathetic dominates the "nighttime" hours by slowing you down. There is a cycle of alertness and awareness in the "daytime," and a "nighttime" cycle of restfulness wherein the muscles relax and many of the reflexes temporarily become dormant. The overall pattern (called circadian rhythm), is also manifested by changes in the endocrine activity and blood constituents. Although it is a deeply rooted phenomenon, we do not as yet know the full scope of its effects, particularly with regard to those flyers who go from one side of the world to the other in a matter of hours, or whose flying frequently alternates between daytime and nighttime missions.

As an occupational group, professional flyers are a healthy lot. In the performance of their duties, however, they must adjust to a number of unusual conditions: extremes of temperature, switching rest cycles, many hours of immobility in the cockpit, constant responsibility, numerous tests and check rides, and marginal weather. To stay on top of such a job requires constant effort. The manner in which a man reacts to the stresses imposed on him depends upon his ability, motivation, and mental and physical fitness. In order to avoid "getting behind the power curve" the flyer needs sufficient rest, a proper diet, adequate exercise, and an avoidance of unnecessary self-imposed stresses.—Aerospace Safety Magazine, Norton Air Force Base, Calif.

PULMONARY PHYSIOLOGY

The Life Sciences Research Group, Aerospace Crew Equipment Department, Naval Air Development Center has been working with a new method of presenting respiratory flow-volume data in pulmonary function assessment. This method involves the placement of an accurate loop tracing on an absolute flow-volume reference grid in one operation. A graphic representation of all lung volumes and peak flows at all volumes is produced. This method is being evaluated in cooperation with the Cardio-Pulmonary Laboratory at the Naval Hospital, Philadelphia, and is expected to aid in the diagnosis of pulmonary diseases.—AeroMed, BuMed.

BLOOD VOLUME MEASUREMENTS

Navy researchers at the Naval Aerospace Medical Institute are investigating methods for proper evaluation of heart-lung performance. One method of making the rapid repeated measurement of the rate of blood volume output by the heart under rest and working conditions is currently under study by Doctor H. H. Khalil of the Institute. This involves the controlled application of heat to the right chamber of the heart with measurements of temperature change as an index of blood volume propelled by the heart. So that almost instant heart-lung performance data may be repeatedly obtained under various conditions of the environment, this technique is being refined. Redesigned equipment now overcomes difficulties in performance caused by physiological activities and increased the rapidity of measurements by thermal dilution. Already applied, this method is being used in a study of the effect of training on the response of greyhounds to exercise. In the future other uses should be available; equipment may be adapted to computerization and telemetry. Also, the method may be applied to chimpanzees and human patients under the various physiological conditions of rest, work, and environmental stress.—AeroMed, BuMed.

EDITOR'S SECTION

A STATEMENT ON NORMAL (WHOLE, POOLED) HUMAN PLASMA

Pooled human plasma has been condemned by a series of recent actions by the National Research Council Committee on Plasma and Plasma Substitutes (NRC) and by the Division of Biologics Standards of the National Institutes of Health (DBS). A statement by the American Association of Blood Banks in response to these actions appears appropriate.

When human plasma is pooled, the possibility that hepatitis virus will be included in the pool increases with the number of units in the pool. Initial experience with pooled human plasma indicated that it carried a high risk of transmitting hepatitis; but the studies of Allen, corroborated by Hoxworth, demonstrated that the risk could be virtually eliminated by prolonged storage at elevated temperatures in the liquid state. A temperature of at least 30 C for a period of at least six months has been generally accepted, and many years of experience with pooled plasma which has been stored under these or more stringent conditions have corroborated the apparent safety of such plasma. A recent survey of blood banks who supply large volumes of this material found that, with one exception, these banks had never received a report of clinical hepatitis in a recipient of appropriately stored pooled plasma (in the absence of other high risk components).

The March-April issue of *Transfusion*, however, contained a report by A. G. Redeker, C. E. Hopkins, B. Jackson and P. Peck, entitled "A Controlled Study of the Safety of Pooled Plasma Stored in the Liquid State at 30-32 C for Six Months," which demonstrated a 10 percent incidence of hepatitis in recipients of pooled plasma only. Redeker's group was able to find cases of hepatitis by careful repeated physical examination, coupled with liver function tests, of recipients of such plasma.

Based on this single study, the NRC published a strong statement concluding that the use of pooled plasma should be "discouraged and even discontinued." The statement pointed out that a safe substitute was available in the form of serum albumin and that there was no evidence pooled plasma had any unique advantages. The NRC statement was published in the same issue of *Transfusion* as the Redeker paper and was released simultaneously to the lay press. Due to a delay in publication of that issue of *Transfusion*, the general press release occurred weeks before the scientific publication. As

a result the medical and blood banking professions were presented with a *fait accompli*. Pooled plasma was condemned before most of the experts who produce and transfuse pooled plasma had seen the evidence. This, of course, is contrary to customary practice in medical science in which data is usually presented at open meetings where objections may be raised, and is published in full detail to permit comments before action based on the data is taken.

The Division of Biologics Standards of the National Institutes of Health (DBS) joined the NRC in its abrupt condemnation of pooled plasma. All holders of licenses for pooled plasma received a telephone call from a representative of the DBS the day before the general press release to alert them to its appearance. Although this was the first notice most of the licensees received of the Redeker study, the DBS representative suggested that they voluntarily relinquish their licenses. Most of the licensees elected to wait until they had the opportunity to read and analyze the data in the Redeker study, and to ascertain whether information to confirm or refute it was available. On May 20, 1968, the DBS issued a memorandum to all holders of a license for Normal Human Plasma notifying them that they were "not to sell or ship this product in interstate or foreign commerce after June 15, 1968" and that "steps will be taken on June 15, 1968 to revoke without prejudice all presently issued licenses." While DBS may properly suspend licenses upon evidence that a product might be unsafe, both DBS regulations and the public interest require appropriate hearings before final action, such as revocation, is taken.

Is the evidence sufficient to warrant outright condemnation of all pooled plasma produced in this country? There are reasons to question this. Redeker's plasma recipients do appear to have been infected with hepatitis virus. How then do we explain the absence of previous reports from the pooled plasma used in this country which had been aged at elevated temperatures? Although Redeker's methods should be expected to uncover many more cases of hepatitis than would be voluntarily reported, those banks depending on voluntary reporting did get reports of cases due to whole blood, but none to pooled plasma. Was the plasma used by Redeker stored under less optimal conditions? Obviously hepatitis virus can be destroyed if the incubation

temperature is hot enough or the time of storage sufficiently prolonged. Albumin can be made safe by incubation for 10 hours at 60 C, a temperature whole plasma will not tolerate. The aging of plasma at elevated temperatures has unquestionably decreased hepatitis incidence (voluntary reporting) from a very high figure to essentially none. Is it possible that 30-32 C for six months provides conditions with an insufficient safety factor?

Many of the blood banks with no reports of hepatitis store their plasma longer than six months, and prepare pools with fewer units and less reliance on paid donors than the commercial suppliers of the plasma used by Redeker. It obviously becomes of crucial importance to be certain that the plasma used by Redeker was stored for at least six months at 30 C or more. There were no regulations requiring this. Unfortunately, neither of the commercial suppliers whose plasma resulted in hepatitis have been able to find records to document that the lots of plasma used were appropriately stored. For all these reasons, then, it seems justifiable to question whether the results with the plasma Redeker used justify condemnation of all pooled plasma prepared in this country.

The NRC statement makes it clear that the committee would be willing to reconsider its recommendation if evidence is presented that more stringent storage conditions can make pooled plasma safe, or if evidence is presented for any unique advantage of pooled plasma. They insist that evidence of the safety of plasma must involve close recipient observation of the type employed by Redeker, with liver function tests and biopsies to detect anicteric cases. Such a study would take years and it is doubtful whether financial support for it would be forthcoming. Similar difficulties stand in the way of collecting evidence on the unique advantages of pooled plasma. Allen has shown that in animals aged pooled plasma can provide total nutrition, in contrast to albumin. The importance of this in human therapy requires documentation. Patients with deficiencies of immunoglobulins can have replacement of the missing IgG fraction by Cohn Fraction II gamma globulin, but IgA and IgM can be provided only in plasma. Allen has concluded that effective immunoglobulins are present in aged plasma, but it is not known whether this includes active IgA and IgM as well as IgG fractions.

If plasma has any unique advantages over albumin, it could, of course, be transfused as single donor plasma, a component not included in the NRC-NIH indictment. Single donor plasma has,

however, the same risk of inducing hepatitis as whole blood. As previously stated, the blood banks who have no voluntary reports of hepatitis due to aged plasma have many reports of hepatitis due to whole blood. Aged plasma cannot be used to supply coagulation factors; but, if it is safer than single donor plasma, it should be available for situations (if any exist) where it has advantages over albumin.

It must be recognized that emergency blood volume replacement, which has been a major indication for aged pooled plasma, can be accomplished equally effectively with serum albumin or electrolyte solutions. No one, including the NRC (whose statement could place all future users of pooled plasma in legal jeopardy) or the DBS (which cut off interstate shipment of pooled plasma as of June 15) has any figures to indicate whether there is enough serum albumin in this country to replace the large amounts of pooled plasma which have been used. At the time of this writing, some plasma processors are unable to fill current orders for albumin. Redeker's study had the serious defect of comparing the incidence of hepatitis due to plasma with that in a much smaller group receiving albumin. He was unable to obtain enough albumin to choose his recipients at random.

We concede that proof of the safety of pooled plasma from other sources will require evidence not now available nor obtainable within a reasonably short period. We believe that the use of aged pooled plasma is still justifiable in situations where albumin is not available or does not meet the requirements for which pooled plasma is being given.—American Association of Blood Banks, Chicago, Ill.

NOTICE TO ACTIVE DUTY MEDICAL, DENTAL, NURSE, AND MEDICAL SERVICE CORPS OFFICERS

It is requested that *active duty officers* refrain from advising the U.S. Navy Medical News Letter of their change of address. These changes are automatically noted in the BUMED distribution list from which our list is derived. Therefore individually submitted change of addresses have resulted in some officers receiving more than one copy of the News Letter.—Editor.

AMERICAN SOCIETY FOR HOSPITAL FOOD SERVICE ADMINISTRATORS

CDR Ernest J. Irvin, MSC USN, Head, Food Service Branch, BUMED has recently been elected to the Board of Directors (member at large) of the

Chesapeake (D.C., Delaware, Maryland and Virginia) Chapter of the American Society for Hospital Food Service Administrators of the American Hospital Association. CDR Irvin had previously served on the committee to formulate by-laws to govern the activities of the newly formed organization. CDR Irvin is also a charter member of the American Society for Hospital Food Service Administrators. —Hospital Admin Div, BuMed.

AMERICAN BOARD CERTIFICATIONS

American Board of Dermatology

LCDR Andrew N. Cattano, MC USN

American Board of Obstetrics and Gynecology

LCDR John H. Hoertz, MC USN

American Board of Otolaryngology

CDR Thomas F. Miller, Jr., MC USN

LCDR Brent A. Welch, MC USN

American Board of Plastic Surgery

CDR James J. Ryskamp, Jr., MC USN

American Board of Psychiatry and Neurology

LCDR Charles W. Erwin, MC USNR

American Board of Radiology

CDR John C. Baxter, MC USN

American Board of Surgery

LCDR James Ellsworth C. Norris, MC USN

American Board of Thoracic Surgery

CDR Carl N. Simpkins, Jr., MC USN

CDR Marion K. Neugebauer, MC USN

American Board of Urology

CDR Hellmut C. Gebhardt, MC USN

LCDR Oran W. Chenault, Jr., MC USN

LCDR William G. Plavcan, MC USN

American College of Preventive Medicine

CAPT Robert O. Peckinpugh, MC USN

In Memoriam

RADM William Dalton Davis, MC USN (Ret)

CAPT Roy W. Tandy, MC USN (Ret)

CAPT Percy N. Willson, DC USN (Ret)

LCDR Leo L. Davis, MC USN (Ret)

LT Joseph A. DeMatteo, MC USN (Ret)

LT John M. McMackin, MSC USN (Ret)

LT Alexander C. Thompson, MC USN (Ret)

NOTE TO ALL ADDRESSEES

The Surgeon General has determined that the U. S. Navy Medical News Letter will appear as a monthly publication instead of biweekly commencing January 1969. In addition the cover has been redesigned to conform to government printing regulations. All materials submitted for publication will appear at the previously stipulated time as each issue will consist of 60 pages instead of 30 pages as previously.

DEPARTMENT OF THE NAVY

BUREAU OF MEDICINE AND SURGERY
WASHINGTON, D.C. 20390

OFFICIAL BUSINESS

PERMIT NO. 1048

POSTAGE AND FEES PAID
DEPARTMENT OF THE NAVY

EDNEWSLZC11

MADIGAN GEN HOSPITAL
MED-TECH LIB
TACOMA WASH 98431

1

M